VISIT…

Carbohydrates

CHAPTER 25

MASTERING ORGANIC CHEMISTRY

- Understanding the General Structures of Carbohydrates
- Understanding the Stereochemistry of Carbohydrates
- Understanding the Cyclization of Monosaccharides to Form Hemiacetal Rings
- Predicting the Products of the Common Reactions of Monosaccharides
- Understanding Fischer's Structure Proof for Glucose
- Understanding the General Structural Features of Disaccharides and Polysaccharides

CARBOHYDRATES ARE IMPORTANT, naturally occurring organic compounds. They include simple sugars, or monosaccharides, such as glucose and fructose, and polysaccharides, such as starch and cellulose, which are more complex compounds composed of a number of sugar units. Carbohydrates are one of the initial products of photosynthesis. As such, they serve as the molecules that store the sun's energy for later use in metabolism. In addition, carbohydrate polymers are structural materials used by plants and animals. Even our genetic material, DNA, contains carbohydrate units as part of its polymeric backbone.

This chapter begins with a discussion of the structure and stereochemistry of monosaccharides. Then the formation of cyclic structures from monosaccharides is discussed. This is followed by the presentation of a small number of reactions of these compounds. The classic series of experiments that was used to establish the structure of glucose is presented next. Finally, the structures of disaccharides, polysaccharides, and a few other types of carbohydrate-containing compounds are introduced.

25.1 STRUCTURES OF CARBOHYDRATES

Many carbohydrates fit the general formula $C_x(H_2O)_x$, so it is apparent how the name originated. Actually, they are polyhydroxy aldehydes or ketones. Glucose, $C_6H_{12}O_6$, is a typical monosaccharide. It is a six-carbon aldehyde with hydroxy groups on all of the other carbons.

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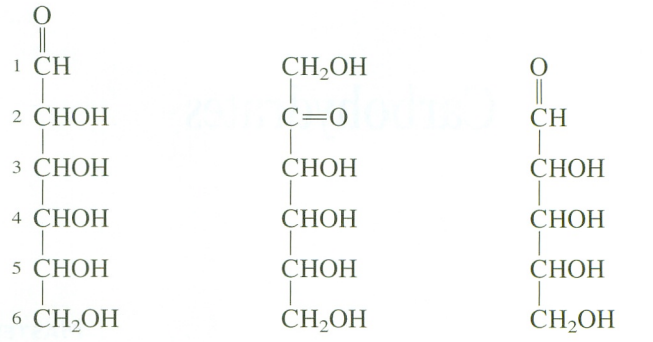


Glucose (an aldohexose) | Fructose (a 2-ketohexose) | Ribose (an aldopentose)

Glucose is an aldohexose, where aldo- indicates that it is an aldehyde, -hex- designates the number of carbons, and -ose is the suffix used for carbohydrates. Some other common monosaccharides are fructose, a 2-ketohexose that is isomeric with glucose, and ribose, an aldopentose that contains one fewer carbons than glucose.

PROBLEM 25.1

Show a structure for ribulose, a 2-ketopentose.

25.2 STEREOCHEMISTRY OF CARBOHYDRATES

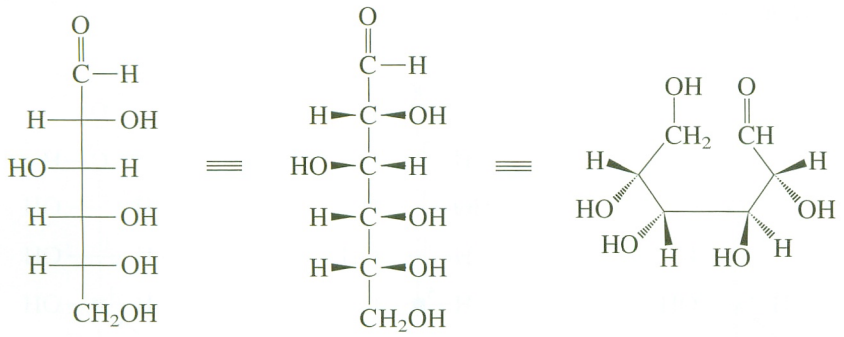
As can be seen by examination of its structure, glucose has four stereocenters, C-2, C-3, C-4, and C-5. Therefore, this structure has $2^4 = 16$ stereoisomers. One of these stereoisomers is glucose, and one is the enantiomer of glucose. The other 14 compounds (seven pairs of enantiomers) are diastereomers of glucose.

PROBLEM 25.2

How many stereoisomeric aldopentoses are possible? How many stereoisomeric 2-ketopentoses are possible?

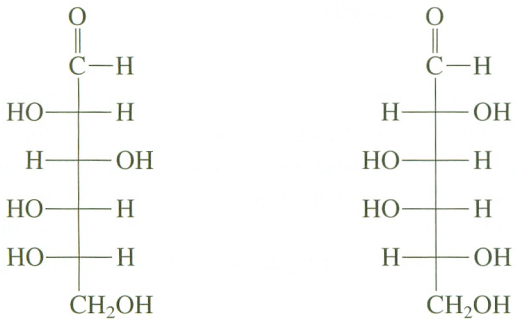
Much of the early research on carbohydrates was done by Emil Fischer, who invented Fischer projections (see Section 7.8) to show the complex stereochemistry of these compounds. Fischer projections have proved quite useful and are still used today. By convention an aldose is drawn with the carbon chain oriented in the vertical direction with the aldehyde carbon on the top. Naturally occurring glucose, designated D-glucose, has the stereochemistry shown in the following Fischer projection (the leftmost structure in the following diagram). Recall that the horizontal bonds in a Fischer projection extend above the plane of the page and the vertical bonds extend below the plane of the page. The middle structure in the diagram shows the horizontal bonds correctly but cannot show all of the vertical bonds projecting below the plane of the page. Although the structure on the right, with all of the carbon–carbon bonds in the plane of

the page, perhaps better represents the shape of glucose, Fischer projections are much easier to use.



D-Glucose
Fischer projection

L-Glucose is the enantiomer of D-glucose and has inverted configuration at all stereocenters. D-Galactose is a diastereomer of D-glucose and differs only in the configuration at C-4.



L-Glucose D-Galactose

The configuration of many biological compounds, including sugars and amino acids, is usually designated by employing the letter D or L, rather than *R* or *S*. These letters relate the configuration to that of the naturally occurring enantiomer of glyceraldehyde, the simplest sugar, which has the D-configuration. By convention the structure is shown with the carbon chain in the vertical direction and with the most oxidized carbon (the one with the most bonds to oxygen) at the top. When written like this, D-glyceraldehyde has the hydroxy group on the right side of the Fischer projection. Any sugar that has this same absolute stereochemistry at its highest-numbered carbon chirality center (at the carbon chirality center farthest from the top) is also designated as having the D-configuration. Thus, the naturally occurring enantiomer of glucose is D because the configuration at C-5 is the same as the configuration of D-glyceraldehyde at C-2; that is, the hydroxy group is on the right side of the Fischer projection. Likewise, D-ribose has the hydroxy group on C-4 on the right side of the Fischer projection. Most sugars that occur naturally have the D-configuration. Note

that D has no relationship to *d*, which designates a compound that is dextrorotatory—that is, one that rotates plane-polarized light in the clockwise or positive direction. Thus, although D-glyceraldehyde and D-glucose are also *d* (or +), D-ribose is levorotatory (*l* or −).

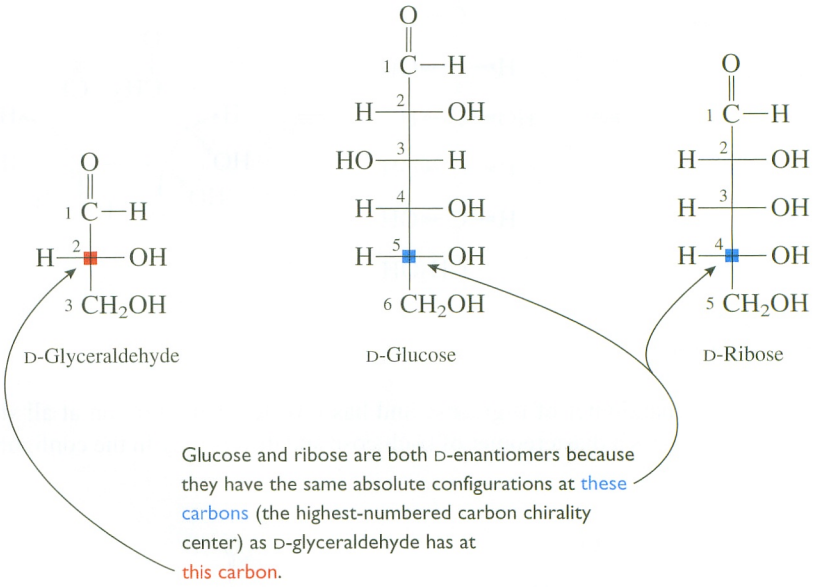
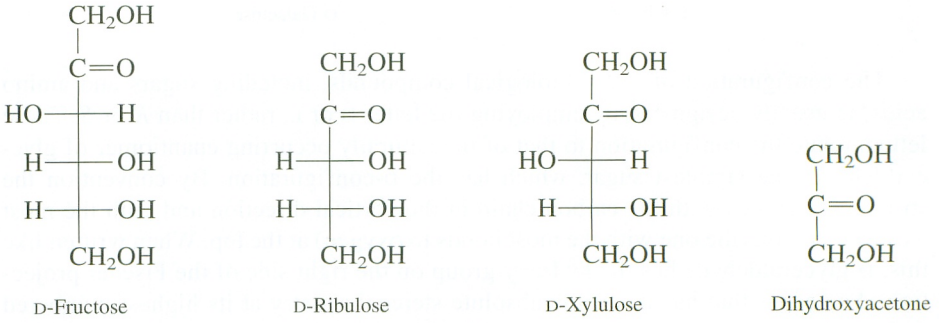

D-Glyceraldehyde
D-Glucose
D-Ribose
Glucose and ribose are both D-enantiomers because they have the same absolute configurations at these carbons (the highest-numbered carbon chirality center) as D-glyceraldehyde has at this carbon.

Figure 25.1 shows all of the possible D-aldoses with three to six carbons. Of these, only D-glucose is commonly found as a monosaccharide in nature. Several others, including D-glyceraldehyde, D-mannose, D-galactose, and D-ribose, are found as part of polysaccharides or in other biological molecules. In addition, the ketoses D-fructose, D-ribulose and D-xylulose (2-ketopentoses with the same configuration at the other carbons as ribose and xylose), and dihydroxyacetone (1,3-dihydroxy-2-propanone) are also common.



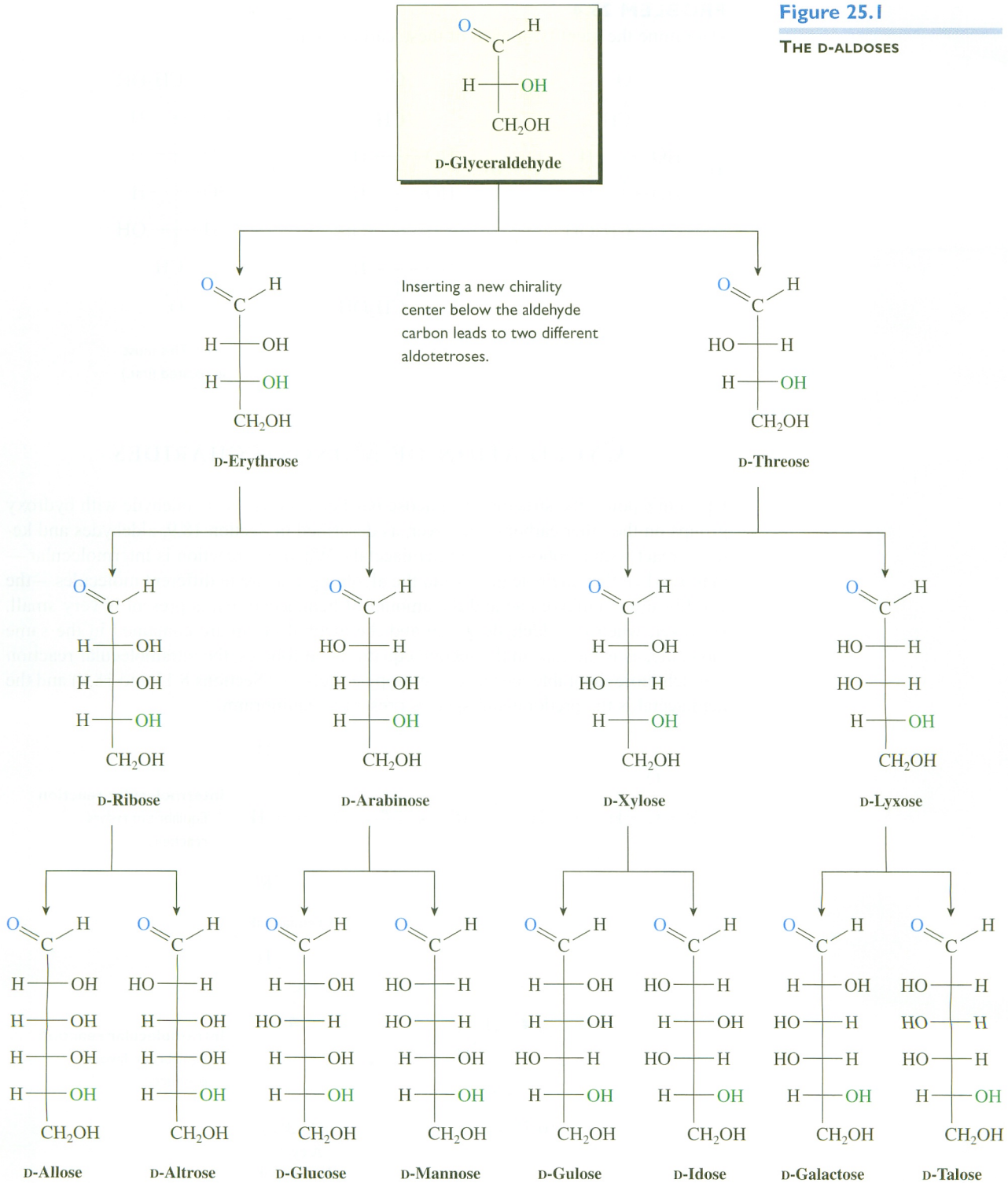
Ketoses

PROBLEM 25.3

Draw Fischer projections for these monosaccharides:

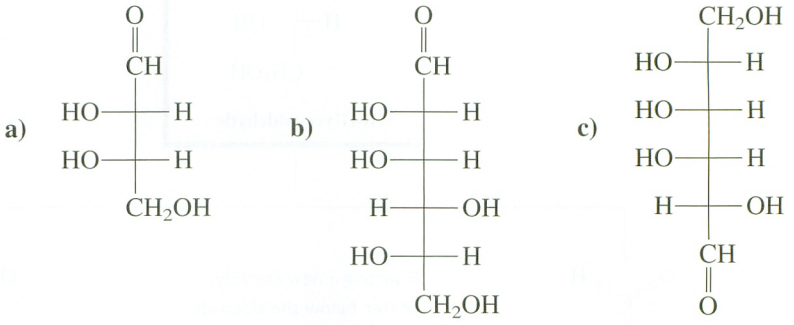
a) L-Glyceraldehyde **b)** L-Mannose

Figure 25.1
THE D-ALDOSES



PROBLEM 25.4

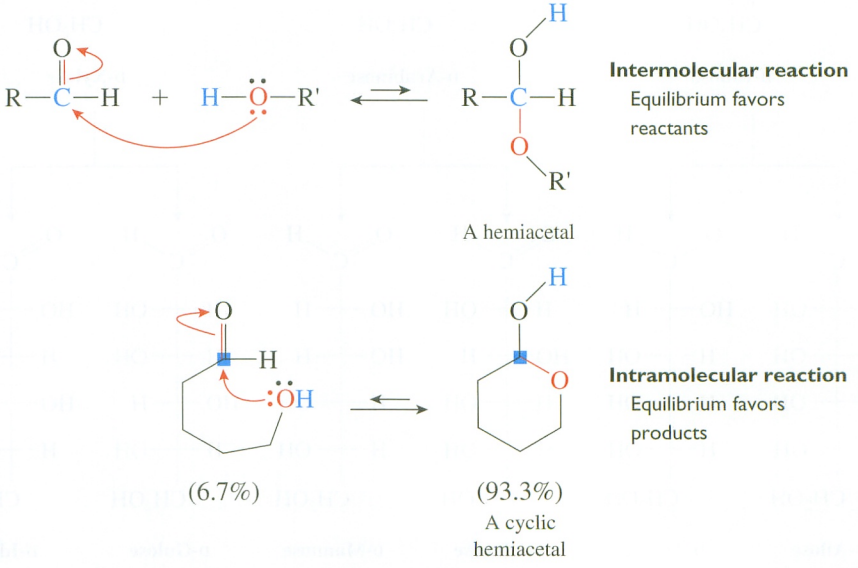
Determine the identity of each of these carbohydrates:



(*Hint:* This must be rotated first.)

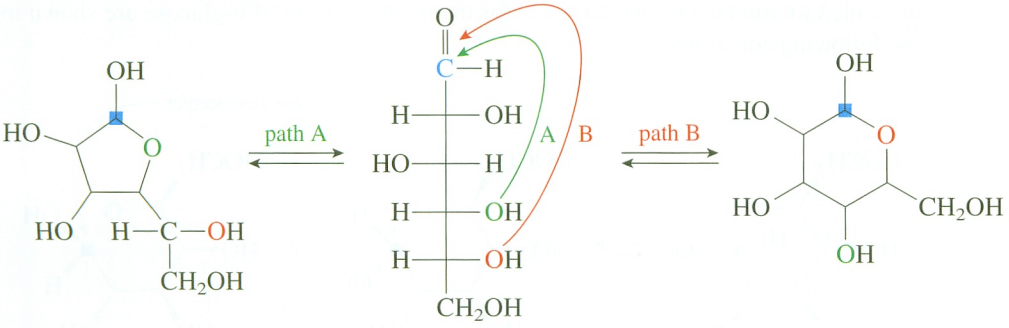
25.3 CYCLIZATION OF MONOSACCHARIDES

Up to this point, the structure of glucose has been shown as an aldehyde with hydroxy groups on the other carbons. However, as described in Section 18.9, aldehydes and ketones react with alcohols to form hemiacetals. When this reaction is intermolecular—that is, when the aldehyde group and the alcohol group are in different molecules—the equilibrium is unfavorable and the amount of hemiacetal that is present is very small. However, when the aldehyde group and the alcohol group are contained in the same molecule, as is the case in the second equation that follows, the intramolecular reaction is much more favorable (because of entropy effects; see Sections 8.13 and 18.9) and the hemiacetal is the predominant species present at equilibrium.



Because glucose and the other monosaccharides contain both a carbonyl group and hydroxy groups, they exist predominantly in the form of cyclic hemiacetals.

Let's consider the cyclization of glucose in more detail. There are five different hydroxy groups that might react with the aldehyde group. However, because five- and six-membered rings are much more stable than others, these are the only ring sizes that need be considered. These two possibilities are illustrated for glucose in the following equation:



<0.2% A furanose | 0.02% D-Glucose | >99.8% A pyranose

The cyclic hemiacetal that has a five-membered ring is called a **furanose.** This name is derived from that of the five-membered, oxygen-containing heterocyclic compound **furan.** The hemiacetal with a six-membered ring is known as a **pyranose** after the heterocycle **pyran.**

Furan Pyran

As we saw in Chapter 6, six-membered rings are generally more stable than five-membered rings, primarily because of increased torsional strain in the latter. Therefore, it is not surprising that the pyranose form of a monosaccharide is usually more stable than the furanose form. At equilibrium, glucose exists primarily as the pyranose (>99.8%), with little, if any, furanose (<0.2%) present. There is also a trace amount (0.02%) of the uncyclized aldehyde present. Of course, this equilibrium depends on the structure of the monosaccharide, and some other sugars have larger amounts of the furanose form.

PROBLEM 25.5

Show the steps in the mechanism for the cyclization of the open form of D-glucose to the pyranose form. (Use the acid-catalyzed mechanism of Chapter 18.)

PROBLEM 25.6

At equilibrium, D-fructose exists 67.5% in the pyranose form, 31.5% in the furanose form, and 1% in the open, uncyclized form. Draw the pyranose and furanose forms. Explain why D-fructose has more of the uncyclized form present at equilibrium than does D-glucose.

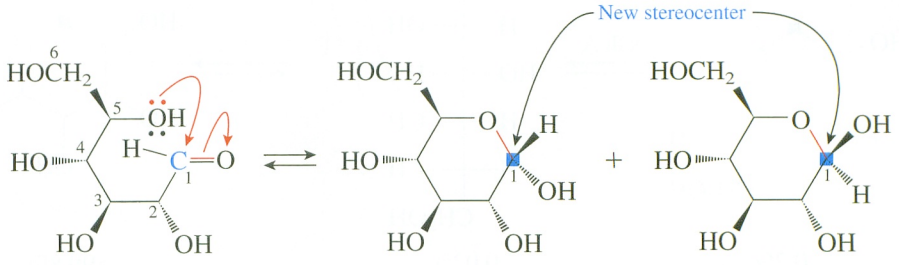
PROBLEM 25.7

How much pyranose form, furanose form, and uncyclized aldehyde would be present at equilibrium for L-glucose?

PROBLEM 25.8

Show the structure of the hemiacetal formed from D-erythrose.

Let's now address the stereochemistry of the cyclization of D-glucose to a pyranose. Note that carbon 1, the hemiacetal carbon, becomes a new stereocenter when the cyclization occurs. Therefore, two diastereomers of the pyranose, with different configurations at the new stereocenter, are formed when D-glucose cyclizes. Such diastereomers are called **anomers.** The two anomers for the pyranose form of D-glucose are shown in the following equation:



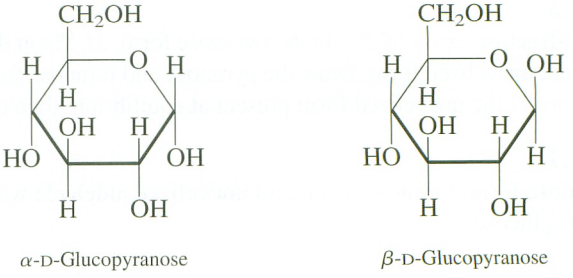
Anomers

By convention, when the sugar is drawn as shown in the preceding equation and the hydroxy group at the new stereocenter projects down, the compound is designated as the α-stereoisomer. When the hydroxy group at the hemiacetal carbon projects up, it is the β-stereoisomer. The full names for these two anomers of glucose are α-D-glucopyranose and β-D-glucopyranose.

PROBLEM 25.9

D-Mannose differs from D-glucose only in its configuration at C-2. Show the formation of α-D-mannopyranose and β-D-mannopyranose from the uncyclized form of D-mannose in the same manner as was done for D-glucose.

Carbohydrate chemists often represent these compounds using **Haworth projections.** In this method the ring is drawn flat and viewed partly from the edge. The bonds to the substituents are shown as coming straight up or straight down from the carbons. Although Haworth projections distort the geometry at the carbons, they are easy to draw and make the stereochemical relationships among the substituents readily apparent.



Haworth projections

PROBLEM 25.10

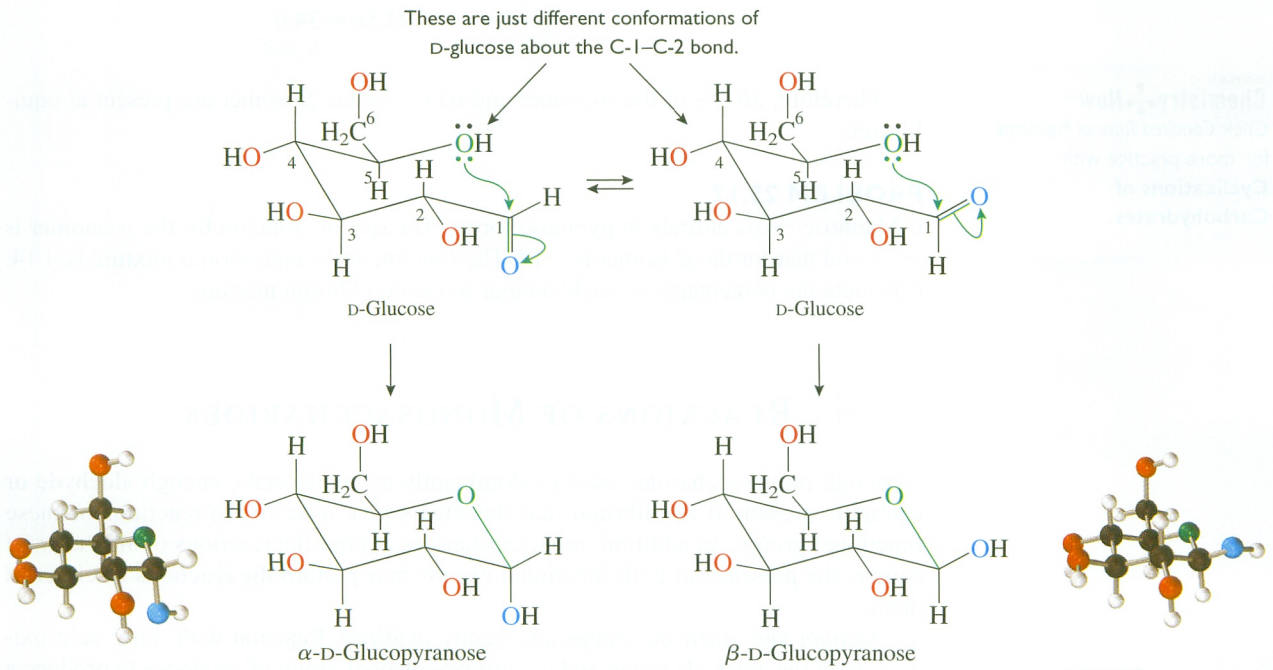
Show Haworth projections for α-D-mannopyranose and its β-anomer. (Remember that D-mannose differs from D-glucose only in its configuration at C-2.)

Haworth projections show the absolute stereochemistries at the various stereocenters of glucose quite well, but the six-membered rings of pyranoses are, of course, not planar. The presence of an oxygen atom in these rings causes only a slight perturbation, so most of the discussion about cyclohexane rings presented in Chapter 6 also applies to pyranose rings. The cyclization of D-glucose to form chair conformations of α- and β-D-glucopyranose is shown in Figure 25.2.

PROBLEM 25.11

Show the chair conformations for α-D-mannopyranose and its β-anomer.

As was the case for cyclohexane derivatives, the chair conformer that has the larger groups equatorial is usually more stable. Therefore, the chair conformers shown in Figure 25.2, which have most or all of the larger substituents equatorial, are more stable than the conformers obtained by ring-flips. The α- and β-anomers differ only in the stereochemistry of the groups at the hemiacetal carbon. In the α-anomer the hydroxy group on this carbon is axial, and in the β-anomer it is equatorial.



Active Figure 25.2

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THE CYCLIZATION OF D-GLUCOSE TO FORM α- AND β-D-GLUCOPYRANOSE. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

Both α-D-glucopyranose and β-D-glucopyranose can be isolated in pure form. Because they are diastereomers, they have different physical properties. For example, the α-stereoisomer has a specific rotation of +112.2, whereas that of the β-isomer is +18.7. However, if either of these pure stereoisomers is dissolved in water, the specific rotation slowly changes, over several hours, to a value of +52.7. This process, termed **mutarotation,** results from the formation of an equilibrium mixture that consists of 36.4% of the α-isomer and 63.6% of the β-isomer. (Of course, the same equilibrium mixture results starting from either of the anomers.) In fact, it is the specific rotation at equilibrium that is used to calculate the equilibrium concentration of the two stereoisomers.

PRACTICE PROBLEM 25.1

Given that the rotation of α-D-glucopyranose is +112.2, the rotation of β-D-glucopyranose is +18.7, and the rotation of an equilibrium mixture of the two anomers is +52.7, calculate the percentages of each anomer present at equilibrium.

Solution

Let x equal the decimal fraction of the α-isomer that is present at equilibrium. Then $1 - x$ equals the decimal fraction of the β-isomer present. The rotations of each must total to +52.7:

$$\begin{aligned} x(+112.2) + (1 - x)(+18.7) &= +52.7 \\ 112.2x + 18.7 - 18.7x &= 52.7 \\ 93.5x &= 34.0 \\ x &= 0.364 \end{aligned}$$

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Therefore, 36.4% of the α-isomer and 63.6% of the β-isomer are present at equilibrium.

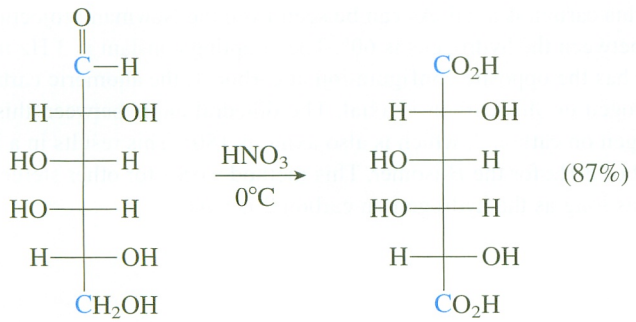
PROBLEM 25.12

D-Mannose exists entirely in pyranose forms. The specific rotation for the α-anomer is +29, and that for the β-isomer is −17. The rotation of the equilibrium mixture is +14. Calculate the percentages of each anomer in the equilibrium mixture.

25.4 Reactions of Monosaccharides

Although monosaccharides exist predominantly as hemiacetals, enough aldehyde or ketone is present at equilibrium that the sugars give most of the reactions of these functional groups. In addition, monosaccharides exhibit the reactions of alcohols. Of course, the presence of both functional groups may perturb the reactions of either of them.

Alcohol and aldehyde groups are readily oxidized. Reaction with nitric acid oxidizes both the aldehyde group and the primary alcohol group of an aldose to produce a dicarboxylic acid. As an example, D-galactose is oxidized to the dicarboxylic acid known as galactaric acid:



D-Galactose Galactaric acid

PROBLEM 25.13

Although D-galactose rotates plane-polarized light, its oxidation product, galactaric acid, does not. Explain.

PROBLEM 25.14

Identify all of the D-aldopentoses from Figure 25.1 that, on oxidation with nitric acid, give diacids that do not rotate plane-polarized light.

Focus On

The Determination of Anomer Configuration

The determination of the configuration at the anomeric carbon of a cyclic sugar such as D-glucopyranose is a difficult problem. Usually, both stereoisomers must be isolated. Then comparison of their properties to those of compounds of known stereochemistry often enables the correct configuration to be determined.

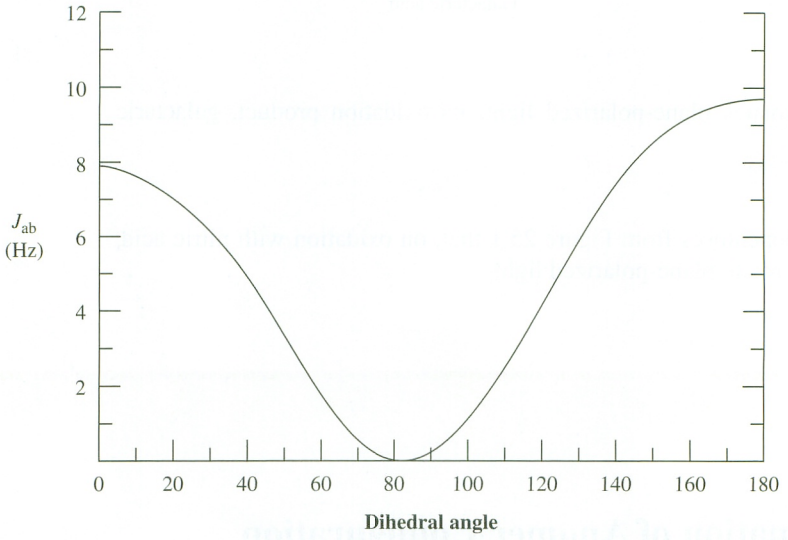
Nuclear magnetic resonance spectroscopy can be used to answer this question in some cases. It has been demonstrated that the coupling constant between two hydrogens depends on their dihedral angle. This relationship, known as the Karplus correlation, is shown on the next page. Note that the coupling constant is maximum at dihedral angles near 180° and is minimum at angles near 90°. In the case of hydrogens on a six-membered ring, this correlation is especially useful. The dihedral angle for axial hydrogens on adjacent carbons is 180°, resulting in a relatively large coupling constant of 8 to 10 Hz. In contrast, if one hydrogen is axial and one is equatorial, or if both are equatorial, then their dihedral angle is 60°. This results in a much smaller coupling constant, usually about 2 to 3 Hz.

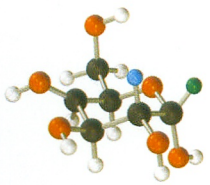
Consider the two anomers α- and β-D-glucopyranose. The peak for the hydrogen on the anomeric carbon, carbon 1, is separated from those for the other hydrogens because of the downfield shift caused by the two electronegative oxygens attached to the carbon. The hydroxy group on carbon 1 of the α-stereoisomer is axial, so the hydrogen on this carbon is equatorial. The hydroxy group on carbon 2 is equatorial, so the

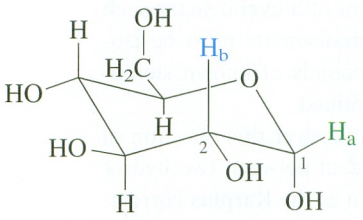
Continued

hydrogen on this carbon is axial. As can be seen from the Newman projections, the dihedral angle between the hydrogens is 60°. The coupling constant is 3 Hz in this case. The β-isomer has the opposite configuration at carbon 1, the anomeric carbon. Therefore, the hydrogen on this carbon is axial. The dihedral angle between this hydrogen and the hydrogen on carbon 2, which is also axial, is 180°. This results in a larger coupling constant of 8 Hz for the β-isomer. This method works for other stereoisomers of glucose also, as long as the hydrogen on carbon 2 is axial.

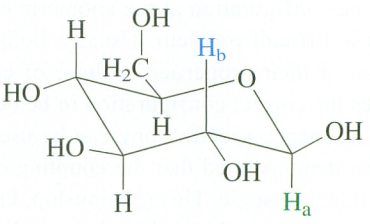
Karplus Correlation



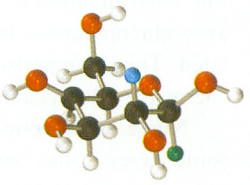


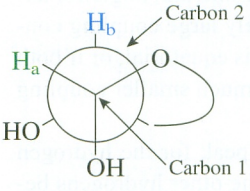


α-D-Glucopyranose

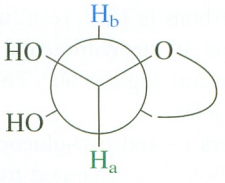


β-D-Glucopyranose



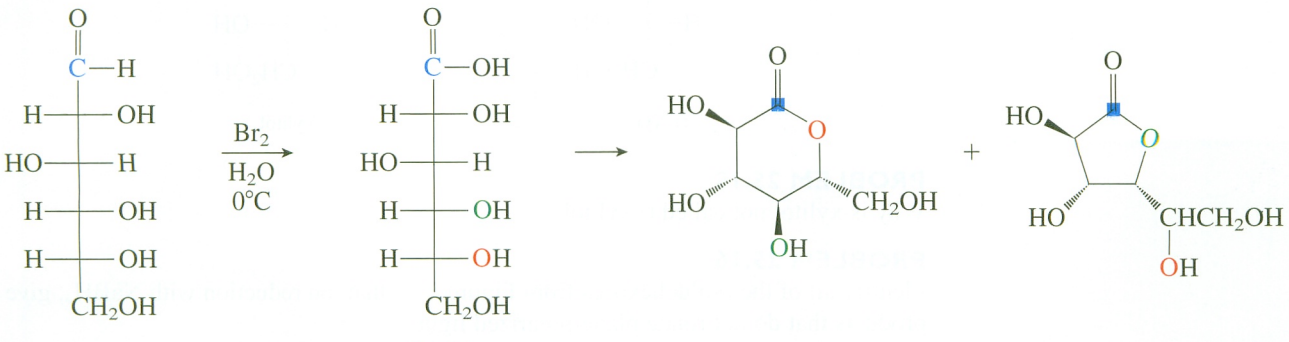


60° dihedral angle
J_{ab} = 3 Hz



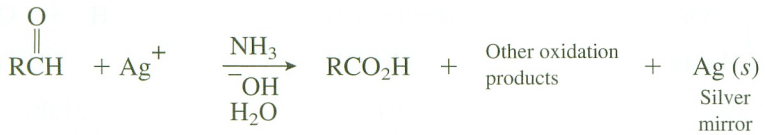
180° dihedral angle
J_{ab} = 8 Hz

It is also possible to selectively oxidize only the aldehyde group with a milder oxidizing agent such as bromine. The oxidation of D-glucose with bromine produces D-gluconic acid in high yield. The reaction of the carboxylic acid group with one of the hydroxy groups to form an intramolecular ester (a lactone) occurs readily. Both five- and six-membered lactone rings can be formed.

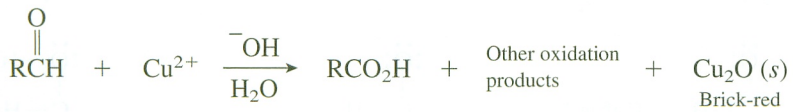


D-Glucose D-Gluconic acid

Oxidation reactions are often used as a test for the presence of an aldehyde group in a carbohydrate. In Tollens' test, the compound is treated with a solution of Ag^+ ion in aqueous ammonia. The aldehyde group is oxidized, and the Ag^+ ion is reduced to metallic silver. The formation of a silver mirror constitutes a positive test. Benedict's test and Fehling's test both employ a solution of Cu^{2+} ion in aqueous base. When the carbohydrate is oxidized, the blue Cu^{2+} ion is reduced to Cu_2O, which forms a brick-red precipitate. (Benedict's reagent has been used in a self-test kit for sugar in the urine caused by diabetes.) Carbohydrates that give a positive test in these reactions are called **reducing sugars** because they reduce the metal ion.

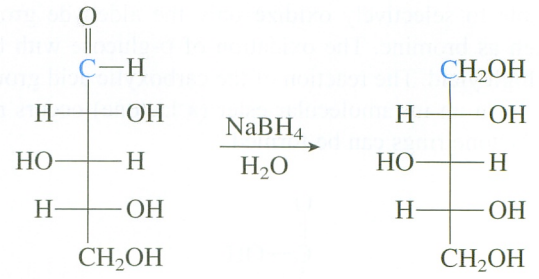


Tollens' test



Benedict's test and Fehling's test

The aldehyde group can be readily reduced by catalytic hydrogenation or with reagents such as sodium borohydride. The reduction of xylose produces xylitol, which is used as a sweetener in "sugarless" gum:



D-Xylose Xylitol

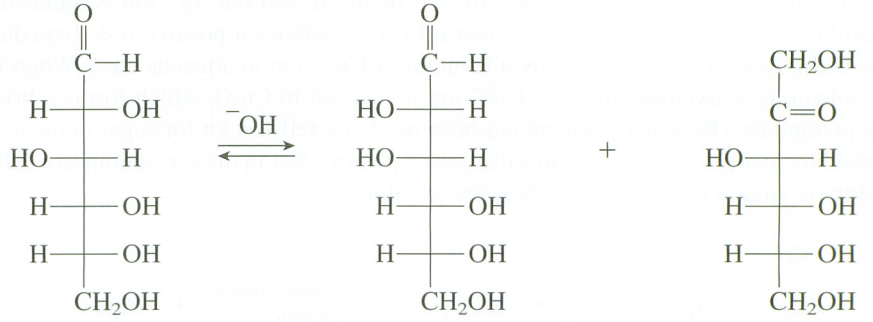
PROBLEM 25.15

Why is xylitol not called D-xylitol?

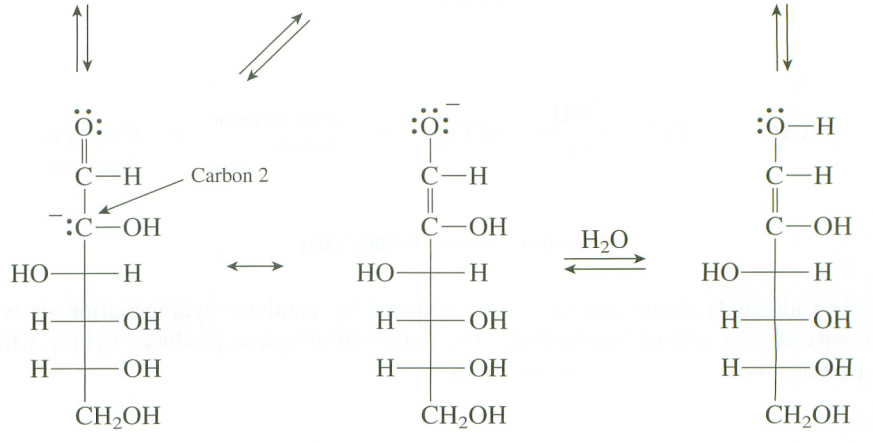
PROBLEM 25.16

Identify all of the D-aldohexoses from Figure 25.1 that, on reduction with $NaBH_4$, give products that do not rotate plane-polarized light.

As is the case with other carbonyl compounds, the carbonyl group of a sugar causes any hydrogens on adjacent carbons to be weakly acidic. This provides a mechanism for the isomerization of sugars in basic solution. Thus, D-glucose is isomerized to D-mannose and D-fructose under basic conditions.



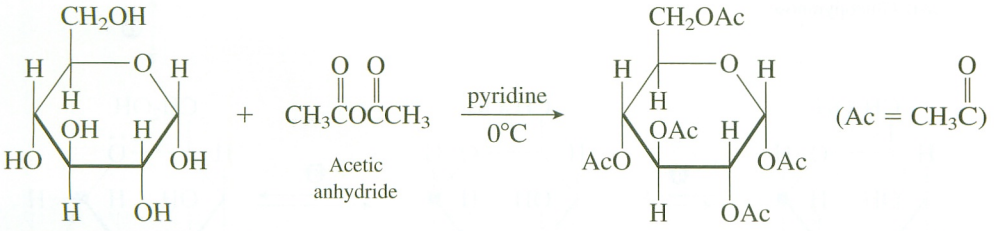
63.5% D-Glucose 2.5% D-Mannose 31.0% D-Fructose



Enolate anion Ene-diol

Base removes an acidic hydrogen on carbon 2 of glucose to produce an enolate anion. Carbon 2 of the enolate anion is planar and is no longer chiral. Protonation from one side regenerates D-glucose while protonation from the other side produces D-mannose, with the opposite configuration at carbon 2. If, instead, the enolate anion is protonated on oxygen, a double bond with a hydroxy group on each carbon, an ene-diol, is formed. Removal of the proton from the hydroxy group on carbon 2 of the ene-diol gives a new enolate ion. Protonation of this enolate ion on carbon 1 produces D-fructose. This is an equilibrium process, so D-fructose is also isomerized to D-glucose and D-mannose under basic conditions. For this reason, D-fructose is also a reducing sugar even though it does not have an aldehyde group.

The alcohol groups of a monosaccharide can be converted to esters by the methods described in Section 19.4. Thus, the reaction of α-D-glucopyranose with acetic anhydride produces a pentaacetate. Note that the hemiacetal hydroxy group is also esterified in this reaction.

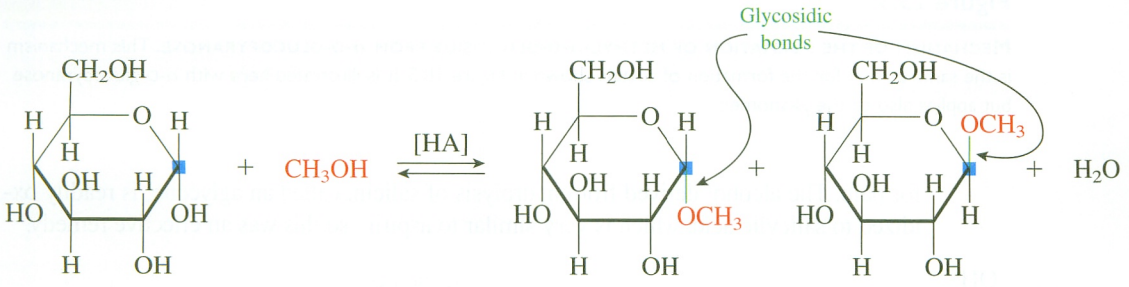


α-D-Glucopyranose 88%

PROBLEM 25.17

If α-D-glucopyranose is reacted with acetic anhydride at 100°C, the major product is the β-isomer of the pentaacetate. Explain how this product is formed.

Perhaps the most important reaction of monosaccharides is the conversion of the hemiacetal to an acetal in the presence of an alcohol and acid. The products are known as **glycosides,** and the bond between the oxygen of the alcohol and the acetal carbon is called a **glycosidic bond.**



(66%) Methyl-α-D-glucoside (32%) Methyl-β-D-glucoside

The mechanism for this reaction is shown in Figure 25.3. It is the same mechanism as that shown in Figure 18.5 on page 776 for the formation of acetals. Because the reaction involves a planar carbocation intermediate, a mixture of stereoisomeric glycosides is formed. This same mixture is produced starting from either α- or β-D-glucopyranose.

Numerous glycosides are found in nature. For example, willow bark contains the glycoside salicin. In ancient Greece, Hippocrates encouraged his patients to chew willow bark

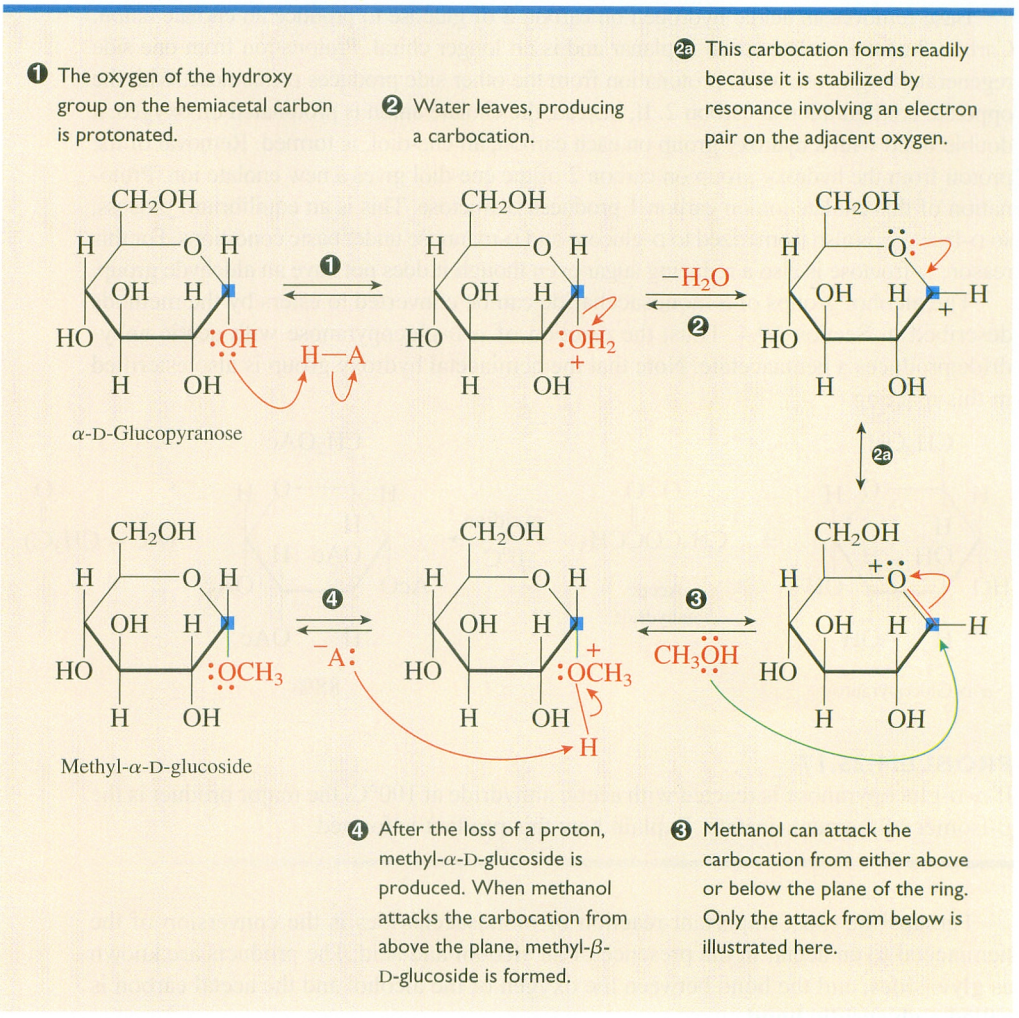
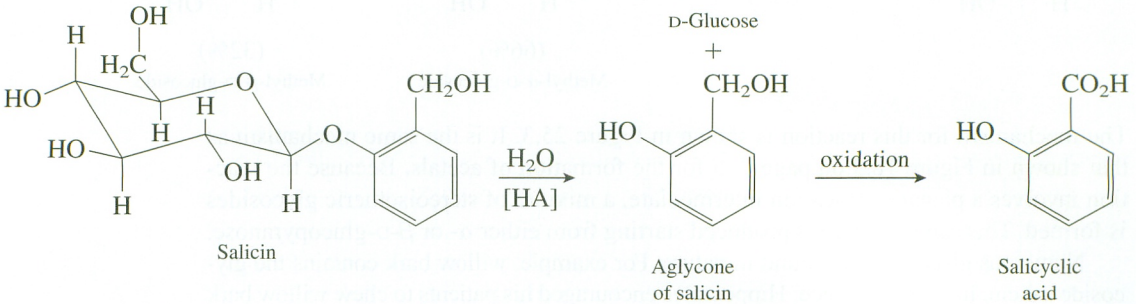

❶ The oxygen of the hydroxy group on the hemiacetal carbon is protonated.
❷ Water leaves, producing a carbocation.
❷a This carbocation forms readily because it is stabilized by resonance involving an electron pair on the adjacent oxygen.
α-D-Glucopyranose
Methyl-α-D-glucoside
❹ After the loss of a proton, methyl-α-D-glucoside is produced. When methanol attacks the carbocation from above the plane, methyl-β-D-glucoside is formed.
❸ Methanol can attack the carbocation from either above or below the plane of the ring. Only the attack from below is illustrated here.

Figure 25.3

MECHANISM OF THE FORMATION OF METHYL-α-D-GLUCOSIDE FROM α-D-GLUCOPYRANOSE. This mechanism is the same as that for the formation of acetals shown in Figure 18.5. It is illustrated here with α-D-glucopyranose but applies also to the β-anomer.

for pain. The alcohol derived from hydrolysis of salicin, called an aglycone, is readily oxidized to salicylic acid, which is very similar to aspirin, so this was an effective remedy.

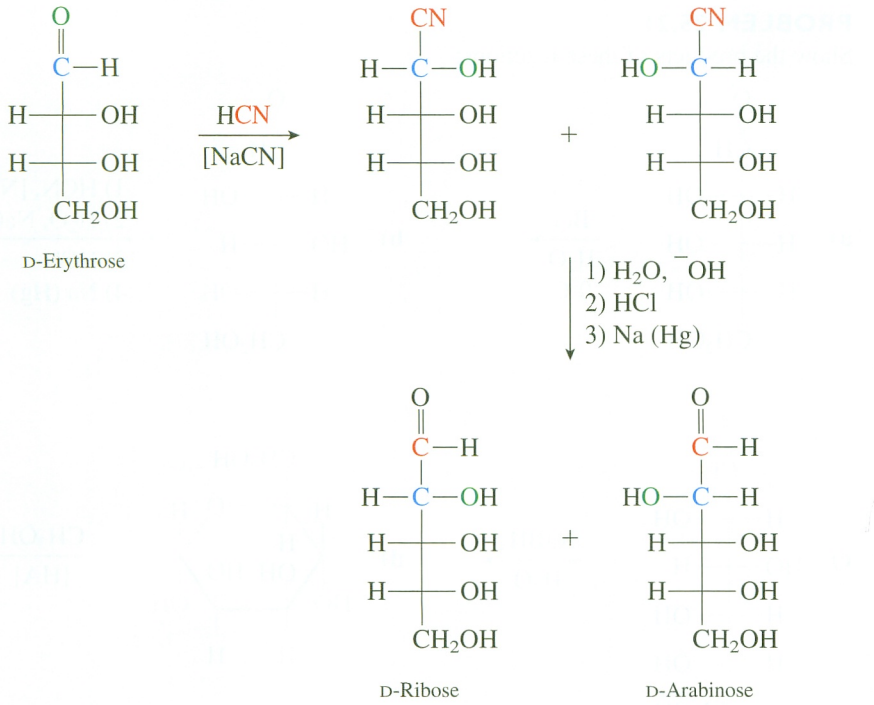


PROBLEM 25.18

Show all of the steps in the mechanism for the hydrolysis of salicin.

The major reason that the formation of glycosides is so important is that disaccharides and polysaccharides are formed from monosaccharide units held together by glycosidic bonds. The oxygen of a hydroxy group from one sugar is used to form a bond to the acetal carbon of another monosaccharide. This process is discussed in Sections 25.6 and 25.7.

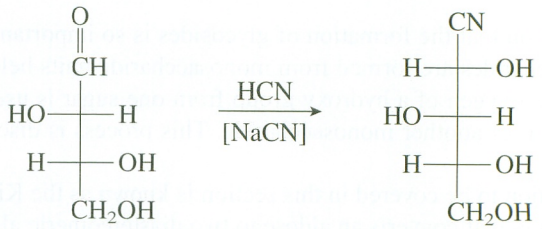
The final reaction to be covered in this section is known as the Kiliani-Fischer synthesis. It is a method that converts an aldose to two diastereomeric aldoses that contain one more carbon than the original sugar. The Kiliani-Fischer synthesis is illustrated in the following reaction sequence, which shows the formation of the aldopentoses D-ribose and D-arabinose from the aldotetrose D-erythrose:



In the Kiliani-Fischer synthesis the starting aldose is first reacted with hydrogen cyanide to form isomeric cyanohydrins (see Section 18.4). This reaction introduces a new stereocenter at the site of the carbonyl carbon of the original aldose. Therefore, the product is a mixture of two diastereomeric cyanohydrins with opposite configurations at the new stereocenter. In the next part of the synthetic sequence, the nitriles are hydrolyzed to carboxylic acids, which spontaneously form lactones. The lactones are reduced to the aldehydes with sodium amalgam. (Today we might choose to accomplish this reduction with some other reagent, such as DIBALH described in Section 19.8.) The overall result is the conversion of the original aldose to two diastereomeric aldoses with one more carbon. The synthesis preserves the configurations of the stereocenters of the original aldose while producing both possible configurations at the new stereocenter, carbon 2 of the aldose products.

PROBLEM 25.19

Show all of the steps in the mechanism for this reaction. What isomeric product is also formed?



PROBLEM 25.20

Show an equation for a Kiliani-Fischer synthesis starting from D-ribose. What are the names of the monosaccharides produced in this reaction?

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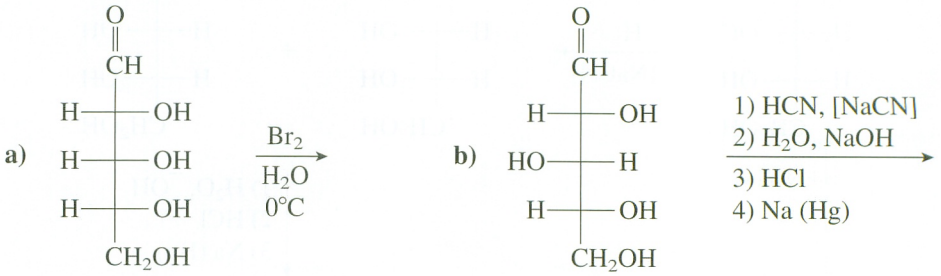
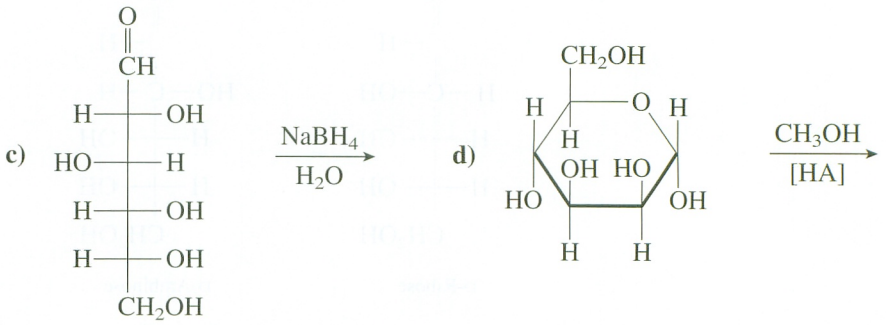
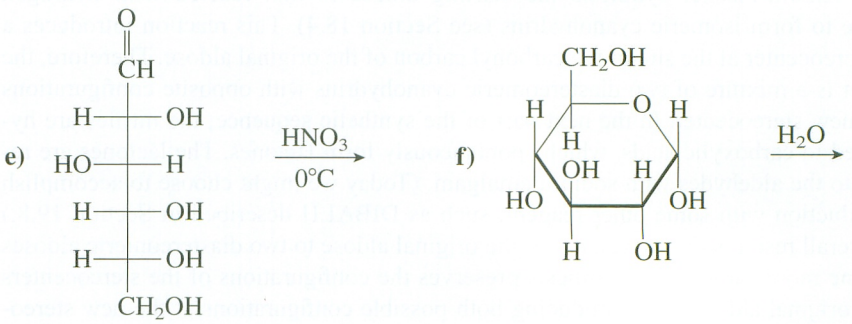
Click *Coached Tutorial Problems* for more practice with **Reactions of Monosaccharides.**

PROBLEM 25.21

Show the products of these reactions:







Focus On

Artificial Sweeteners

Roses are red, violets are blue, sugar is sweet, and so are—many other organic compounds. For example, many compounds that have hydroxy groups on adjacent carbons have a sweet taste. The simplest of these is ethylene glycol or 1,2-ethanediol, the main component of antifreeze. Although this diol is sweet, it is also toxic. Every year, numerous cases of poisonings occur when animals, especially dogs, ingest antifreeze that was carelessly discarded.

Xylitol, another polyhydroxy compound, is used as a sweetener in "sugarless" gum. It has approximately the same number of calories per gram as does sucrose and is not a low-calorie sweetener. However, because it does not have a carbonyl group, it is not fermented by bacteria in the mouth and does not promote tooth decay.

In recent years there has been a great search for a safe, calorie-free sweetener to help diabetic people who need to control their sugar intake and, more recently, to meet the demands of health- and diet-conscious consumers. One such sweetener that was marketed in the late 1960s was calcium cyclamate. However, cyclamates were banned in the United States in 1970 because of a suspected link with cancer.

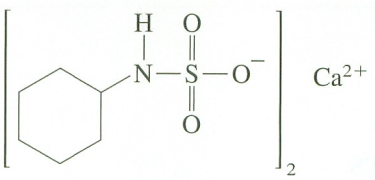
Saccharin is 300 times as sweet as sucrose on a weight basis. Like cyclamate, it is a low-calorie sweetener, not because it has fewer calories than sucrose on a weight basis, but because it is so much sweeter that only a small amount need be used. Saccharin is another artificial sweetener that is suspected of causing cancer in laboratory animals at very high doses. Although the U.S. Food and Drug Administration (FDA) moved to prohibit the use of saccharin in the late 1970s, the ban was blocked by Congress because saccharin was the only artificial sweetener available at that time. Although it has been used for many years now, it has only recently been removed from the government's list of human carcinogens.

The sweetener aspartame was discovered in 1965 and approved by the FDA in 1981. It is the methyl ester of a dipeptide formed from the amino acids aspartic acid and phenylalanine. Because both of these amino acids occur naturally and are part of nearly every protein, there is much less reason to be concerned about the health effects of this compound. Nevertheless, it has been extensively tested. Aspartame is about 180 times sweeter than sucrose, so the amount that is needed to sweeten a can of a soft drink, for example, is so small that it contributes only negligible calories to the diet. In addition, the taste profile of aspartame is much closer to sugar than is that of saccharin. Aspartame, sold under the brand name NutraSweet, has been an enormous financial success. Sucralose (Splenda) is prepared from sucrose by replacing some of the hydroxy groups with chlorines. Its taste closely resembles sucrose, but it is about 600 times sweeter. Acesulfame K (Sunett, Sweet One) is about 200 times sweeter than sucrose. It is quite stable to heat, so it is potentially very useful in baked goods.

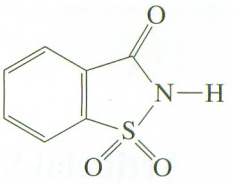
As might be expected, the search for an even better artificial sweetener continues. Alitame is a dipeptide formed from aspartic acid and alanine, with an unusual amide at the carboxylate end of the alanine. It is 2000 times as sweet as sucrose—1 pound of alitame has the sweetening power of 1 ton of sucrose! In addition, because an amide bond is more stable than an ester bond, alitame is more stable to hydrolysis than is aspartame. Therefore, alitame keeps its sweetness in aqueous solution better than aspar-

Continued

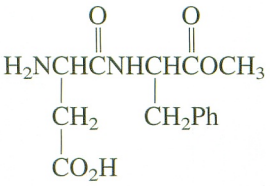
Some Artificial Sweeteners
Numbers in parentheses indicate how much sweeter than sucrose these compounds are.



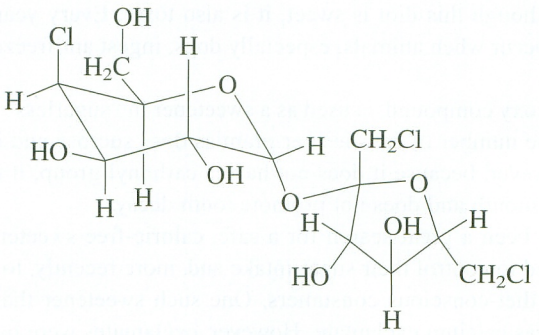
Calcium cyclamate



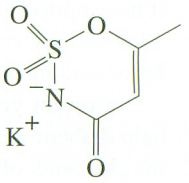
Saccharin
(300×)



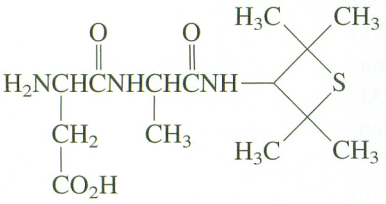
Aspartame
(180×)



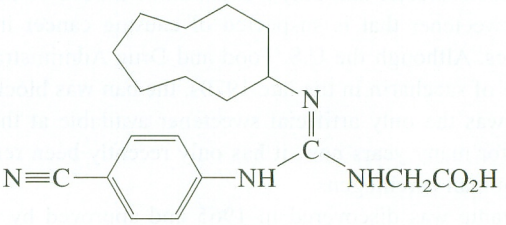
Sucralose
(600×)



Acesulfame K
(200×)



Alitame
(2000×)



Sucrononic acid
(200,000×)

tame does. Even sweeter compounds have been discovered. For example, sucrononic acid is 200,000 times as sweet as sucrose. Neither alitame nor sucrononic acid has yet been approved for use.

Obtaining approval for the use of a new artificial sweetener is a very expensive proposition and requires considerable expenditure of time and scientific effort. This is absolutely necessary, though, because the number of people that would be exposed to products containing the sweetener is so large. (Of course, the fact that most products would contain only a very small amount of an artificial sweetener somewhat decreases the potential for problems.) In addition, certain groups, such as diabetic people, might have consumption patterns that are much higher than other parts of the population. Although obtaining FDA approval is extremely expensive, we may indeed see the approval of other artificial sweeteners in the future because the financial rewards are potentially so large.

Examination of the structures of these sweet compounds does not reveal any simple pattern for their structural features. Chemists are still attempting to determine what it is that makes a compound sweet. They are also trying to model the taste receptor that is responsible for detecting sweetness. Although some progress has been made in this area, there is still a long way to go.

Because of this difficulty in predicting what features are necessary for a compound to taste sweet, most of the discoveries of artificial sweeteners have been serendipitous. In fact, many of the early discoveries resulted from dangerous laboratory practices that we would not condone today. For example, the sweetness of saccharin was discovered in 1879 by a chemist who spilled some of the compound on his hand. Later, while eating lunch in the laboratory, he noticed the extremely sweet taste. The sweetness of cyclamate was discovered in 1937 by a chemist who tasted it on a cigarette that he had set on the lab bench. And aspartame was found to be sweet by a chemist who got some on his hand and later licked his finger before picking up a piece of paper. This resulted in a billion-dollar-per-year product!

The unsafe nature of these practices needs to be emphasized. Precautions should always be taken to minimize exposure to all laboratory compounds. Hands should be washed whenever a compound is spilled on them. Eating, drinking, and smoking in the laboratory are all extremely unsafe practices and should be forbidden. Even licking a finger to pick up a piece of paper should be avoided.

25.5 FISCHER'S STRUCTURE PROOF FOR GLUCOSE

Consider the problem that Emil Fischer faced in the late 1800s. Using a number of experimental observations, he had determined that glucose was an aldohexose. But which of the 16 possible aldohexoses was it? How could the configuration at each of the stereocenters of glucose be determined experimentally? Fischer realized that it was impossible at that time to determine the absolute configuration of a compound—that is, which enantiomer it was. Therefore, he had no way to determine whether glucose was a D-aldohexose or an L-aldohexose. Because he needed to be able to write something for the structures of the compounds he was working with, he arbitrarily chose the D-configuration for glucose. Although this guess was fortuitously correct, it had no bearing on the experiments and the logic that he used to solve the problem. The experiments established the configuration of carbons 2, 3, and 4 *relative* to that at carbon 5, and on the basis of these experiments, Fischer proved that glucose was either the compound shown in Figure 25.1 or its enantiomer.

Fischer studied carbohydrates for many years and performed numerous experiments. Overall, several subsets of these experiments can be used to establish the structure of glucose. Although the ones described here are not the exact ones that he used in the structure proof that he published, they serve to illustrate his reasoning and are somewhat simpler to follow.

There are eight possible structures for D-glucose (see structures **5** through **12** in Figure 25.4). Its actual structure can be determined by using two reactions, oxidation

with nitric acid and the Kiliani-Fischer synthesis, along with the monosaccharides glucose, mannose, and arabinose and one additional sugar. Let's see how this was done.

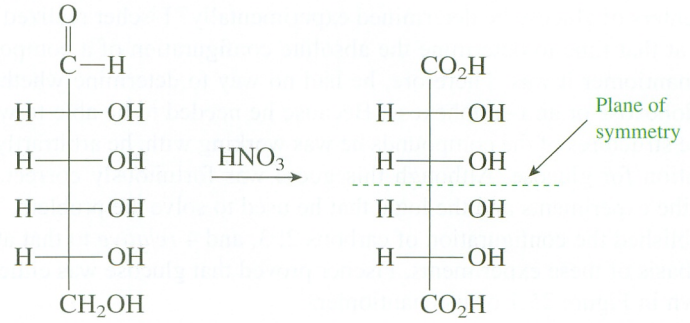
Experiment 1

Application of the Kiliani-Fischer synthesis to the aldopentose D*-arabinose produces aldohexoses* D*-glucose and* D*-mannose.* Because the Kiliani-Fischer synthesis incorporates the stereocenters of D-arabinose without changes, D-glucose and D-mannose must have the same configurations at carbons 3, 4, and 5 as does D-arabinose at carbons 2, 3, and 4, respectively. Furthermore, D-glucose and D-mannose must differ only in their configuration at carbon 2.

The four possible D-aldopentoses are shown as structures **1** through **4** in Figure 25.4. One of these is D-arabinose. Each of these produces two of the eight possible D-aldohexoses on application of the Kiliani-Fischer synthesis. Note that in each case the configurations of the aldohexoses at carbons 3, 4, and 5 are the same as those of the aldopentose at carbons 2, 3, and 4, respectively. If D-arabinose has structure **1,** then the two aldohexoses produced from it upon Kiliani-Fischer synthesis, **5** and **6,** must be D-glucose and D-mannose. Similarly, if D-arabinose is **2,** then D-glucose and D-mannose must be **7** and **8,** and so forth.

Experiment 2

On oxidation with nitric acid, both D*-glucose and* D*-mannose produce diacids that rotate plane-polarized light.* This experiment enables some of the aldohexoses to be eliminated as possibilities for D-glucose and D-mannose. For example, consider the oxidation of aldohexose **5,** shown in the following equation:



5 A diacid

Examination of the structure of the diacid product shows that it has a plane of symmetry. It does not rotate plane-polarized light because it is a meso compound and is not chiral. Therefore, neither D-glucose nor D-mannose can have structure **5.** Because neither can have structure **5,** then, on the basis of experiment 1, the other cannot have structure **6,** nor can D-arabinose have structure **1.**

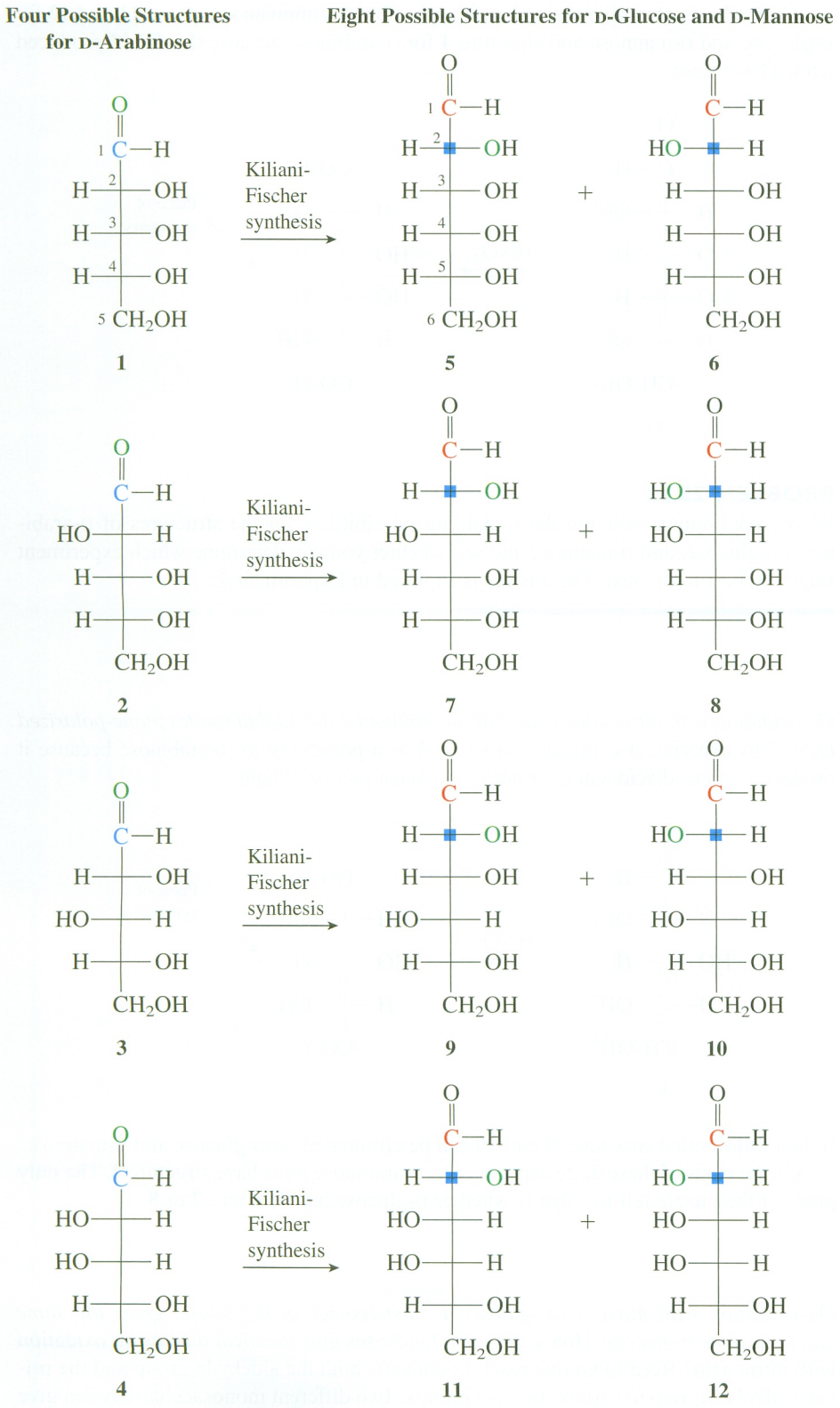
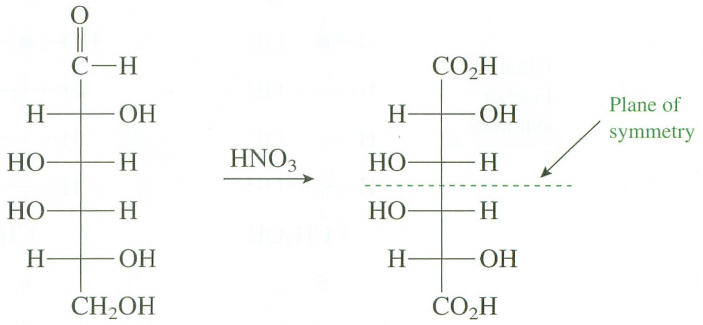


Figure 25.4

POSSIBLE STRUCTURES FOR D-ARABINOSE AND ITS KILIANI-FISCHER PRODUCTS, D-GLUCOSE AND D-MANNOSE.

On the basis of similar reasoning, it is possible to eliminate structures **11** and **12** for D-glucose and D-mannose and structure **4** for D-arabinose because the diacid produced from **11** is meso:



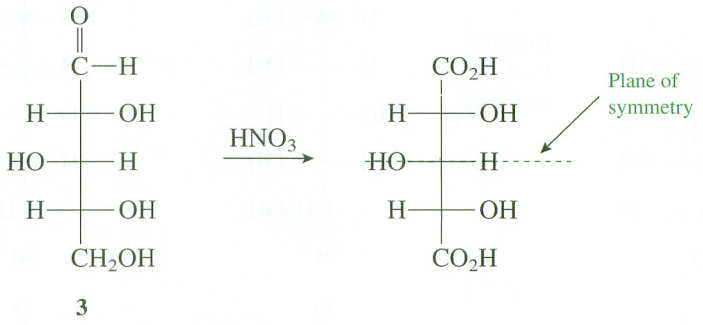
11

PROBLEM 25.22

Before continuing, examine the remaining possibilities for the structures of D-arabinose, D-glucose, and D-mannose and see whether you can determine which experiment might be best to do next. The answer is supplied in Experiment 3.

Experiment 3

On oxidation with nitric acid, D-arabinose produces a diacid that rotates plane-polarized light. This experiment eliminates structure **3** as a possibility for D-arabinose because it produces a meso diacid that does not rotate plane-polarized light:



3

It then follows that structures **9** and **10** can be eliminated for D-glucose and D-mannose.

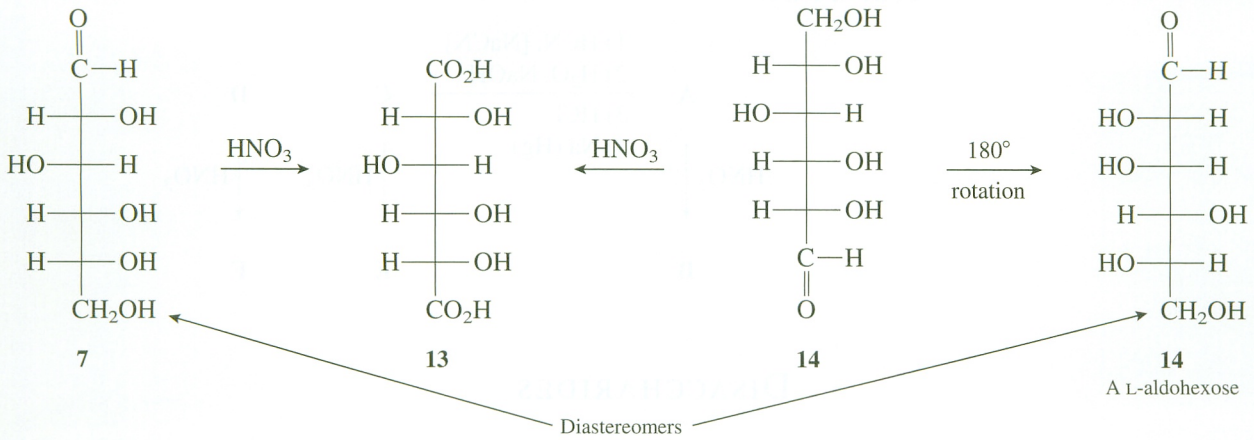
On the basis of these three experiments, D-arabinose must have structure **2.** The only piece of the puzzle left to solve is whether D-glucose has structure **7** or **8.**

Experiment 4

On oxidation with nitric acid, gulose, a diastereomer of D-glucose, gives the same diacid as does D-glucose. How can two aldohexoses give identical diacids on oxidation with nitric acid? Recall that this reaction converts both the aldehyde group and the primary alcohol group to carboxylic acid groups. Two different monosaccharides can give

the same product if they have the same configurations at the asymmetric carbons when one is written with its aldehyde group at the top of the structure and its primary alcohol group at the bottom and the other is written with its primary alcohol group at the top and its aldehyde group at the bottom.

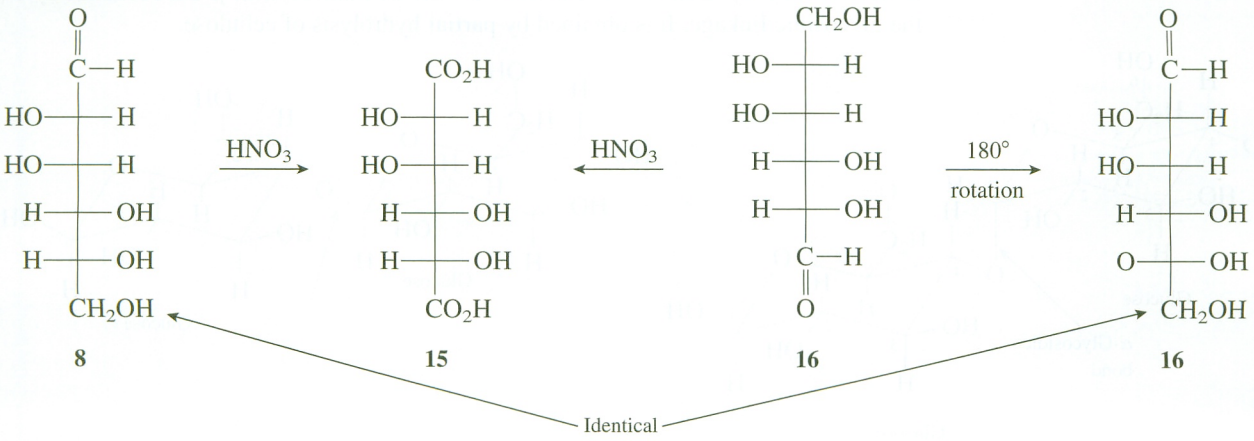
This is best seen with an example. Consider aldohexose **7,** one of the structures remaining as a possibility for D-glucose. On oxidation with nitric acid, **7** produces diacid **13:**



7 **13** **14** **14**
A L-aldohexose

Aldohexose **14,** written with its primary alcohol group at the top of the chain and its aldehyde group at the bottom, also produces diacid **13** on oxidation with nitric acid. A rotation of 180° in the plane of the page (recall that such a rotation of a Fischer projection does not change the configuration of the compound) puts **14** in the more common form with the aldehyde group at the top of the chain. When drawn this way, it is apparent that **14** is an L-aldohexose and is a diastereomer of **7.**

The other possible structure for D-glucose is **8.** Oxidation of **8** gives diacid **15:**



8 **15** **16** **16**

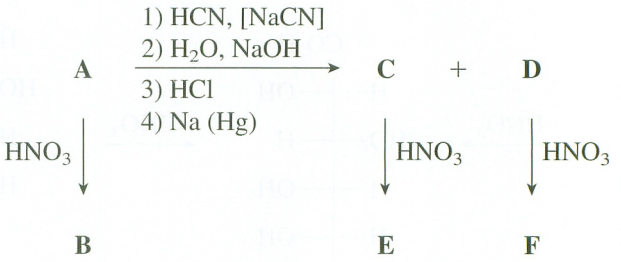
Aldohexose **16** also produces **15** on oxidation with nitric acid. When **16** is rotated 180°, it is found to be identical with **8.** There is only one aldohexose that produces **15** on oxidation!

The structure proof for D-glucose is now complete. If D-glucose were **8,** then the diacid obtained from it on oxidation with nitric acid must be **15.** This is impossible because there is no other aldohexose that produces **15** on oxidation with nitric acid—there

is no possible structure for gulose. Therefore, D-glucose must have structure **7**, and D-mannose has structure **8.** Gulose has structure **14** and has the L-configuration.

PROBLEM 25.23

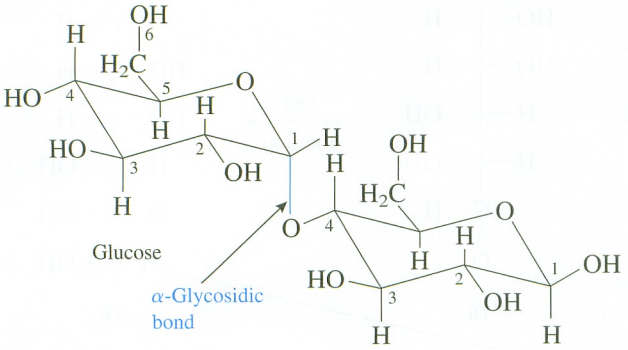
Monosaccharide **A** in the following scheme is a D-aldotetrose. Compound **E** does rotate plane-polarized light, whereas compounds **B** and **F** do not. Show the structures of **A, B, C, D, E,** and **F.**



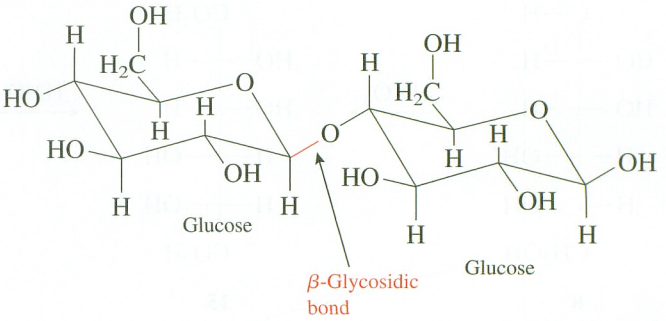
25.6 DISACCHARIDES

Disaccharides are formed from two monosaccharide units that are connected by a glycosidic bond. Different disaccharides result from the combination of different monosaccharides, from the formation of the glycosidic bond using different hydroxy groups on the monosaccharides, or from different stereochemistries of the glycosidic bond. A few of the more important disaccharides are described in the following paragraph.

Maltose is a disaccharide obtained from the partial hydrolysis of starch. It is composed of two molecules of glucose that are linked by a glycosidic bond from the hydroxy group on carbon 4 of one of the glucose units to carbon 1 of the other with α-stereochemistry. Cellobiose is a stereoisomer of maltose with β-stereochemistry at the glycosidic linkage. It is obtained by partial hydrolysis of cellulose.



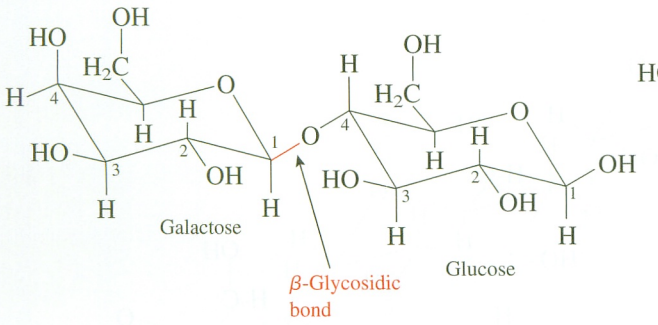
Maltose



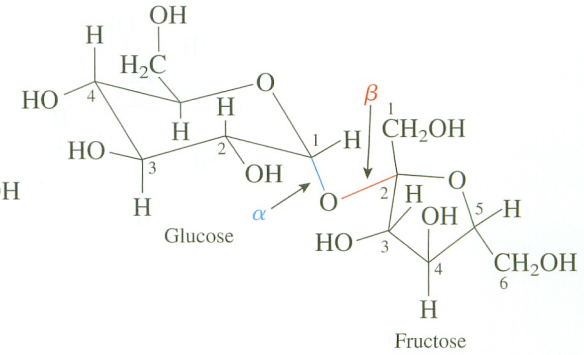
Cellobiose

Lactose, a disaccharide found in milk, is composed of D-galactose and D-glucose, which are joined by a β-glycosidic linkage from the hydroxy group on carbon 4 of glucose to carbon 1 of galactose. Sucrose, also known as table sugar, is the most abundant disaccharide. It is composed of one molecule of D-glucose and one of D-fructose. It differs from the other disaccharides in that its glycosidic bond is formed between carbon 1 (the

acetal carbon) of glucose and carbon 2 (the acetal carbon) of fructose. Because of this connection, it has no hemiacetal group but has two acetal groups instead. The glucose is a pyranose ring with an α-glycosidic bond, whereas the fructose is a furanose ring with a β-glycosidic bond:



Lactose



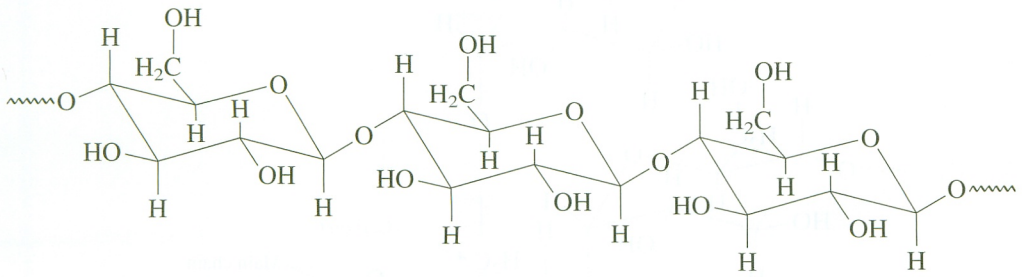
Sucrose

PROBLEM 25.24

Maltose, cellobiose, and lactose are reducing sugars, but sucrose is not. Explain.

25.7 POLYSACCHARIDES

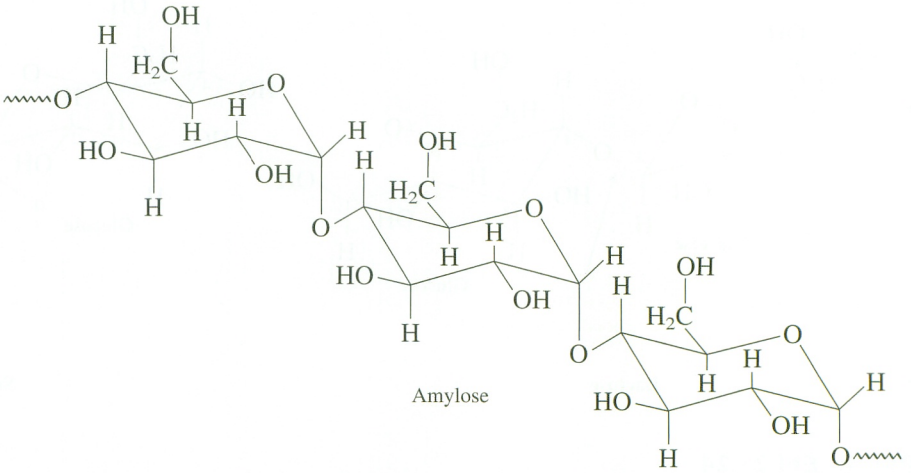
The polysaccharides cellulose, starch, and glycogen are all polymers of D-glucose units linked by glycosidic bonds. Cellulose is the major structural component of the cell walls of plants and is the most abundant organic compound on Earth, accounting for more than half of the carbon in the biosphere. More than 10^{15} kg of cellulose are synthesized and degraded annually. It is a linear polymer containing 2500 to 15,000 D-glucose units linked by β-glycosidic bonds between carbons 1 and 4. As mentioned previously, incomplete hydrolysis of cellulose produces the disaccharide cellobiose, which therefore has the same stereochemistry at its glycosidic bond as does cellulose.



Cellulose

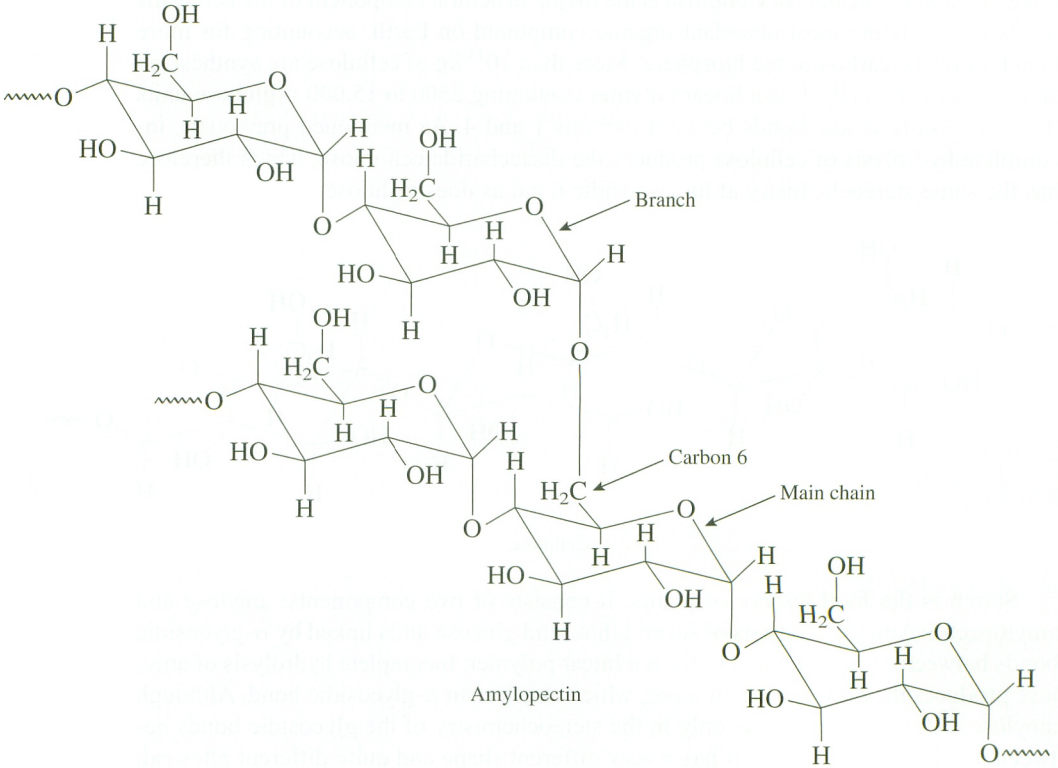
Starch is the food reserve of plants. It consists of two components: amylose and amylopectin. Amylose consists of several thousand glucose units linked by α-glycosidic bonds between carbons 1 and 4 to form a linear polymer. Incomplete hydrolysis of amylose produces the disaccharide maltose, which also has an α-glycosidic bond. Although amylose differs from cellulose only in the stereochemistry of the glycosidic bonds between its glucose monomers, it has a very different shape and quite different physical,

chemical, and biological properties. For example, starch can be digested by almost all animals, whereas cellulose can be digested by only a few microorganisms. In the digestive tracts of herbivores, symbiotic microorganisms hydrolyze cellulose to glucose, using enzymes known as cellulases.



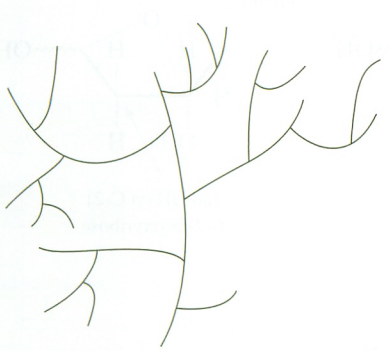
Amylose

The other component of starch, amylopectin, contains up to 10^6 glucose units. It is similar to amylose in that the glucose monomers are connected by α-glycosidic bonds between carbons 1 and 4. It differs, however, in that it has branches that occur every 20 to 30 glucose units. These branches are also amylose-type chains that are connected to the main chain by an α-glycosidic bond from carbon 1 of the branch to carbon 6 of the main chain:

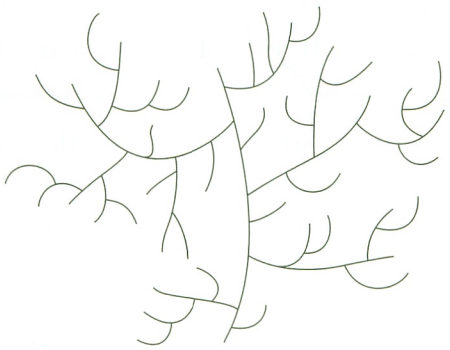


Amylopectin

Branches occur on the branches also, so amylopectin has a treelike structure. Glycogen, the food reserve of animals, has a structure similar to that of amylopectin except that it has branches every 8 to 10 glucose units. The structures of these two polymers are represented schematically in the following drawings:

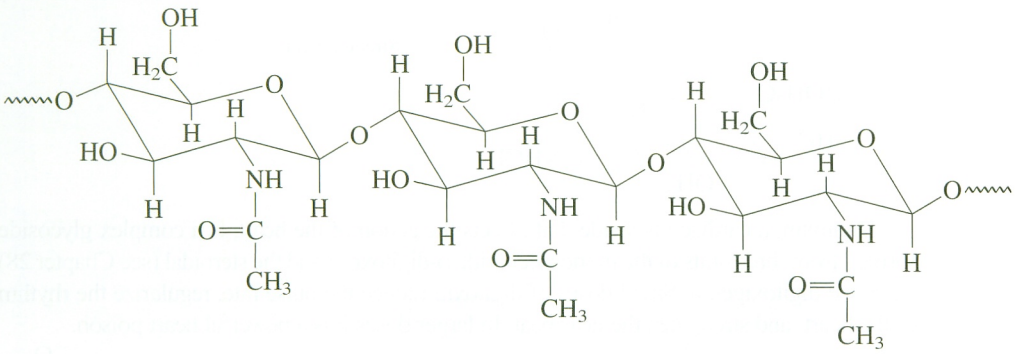


Amylopectin



Glycogen

Chitin, which is the structural component of the exoskeleton of invertebrates such as crustaceans, insects, and spiders, resembles cellulose with the exception that the hydroxy groups on carbon 2 are replaced by acetylamino groups.

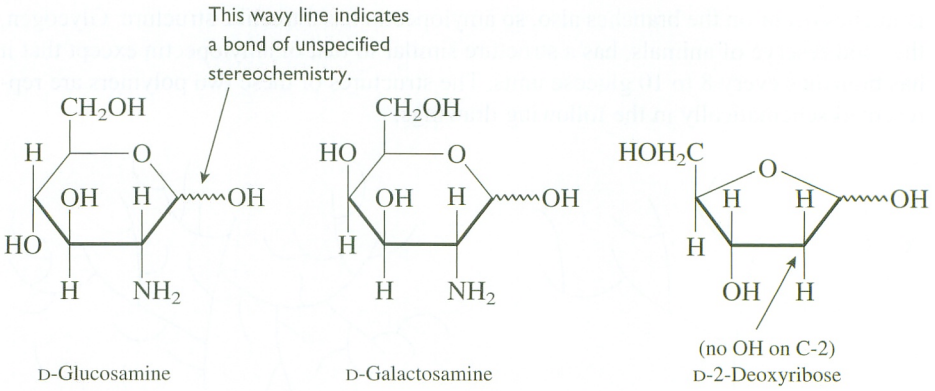


Chitin

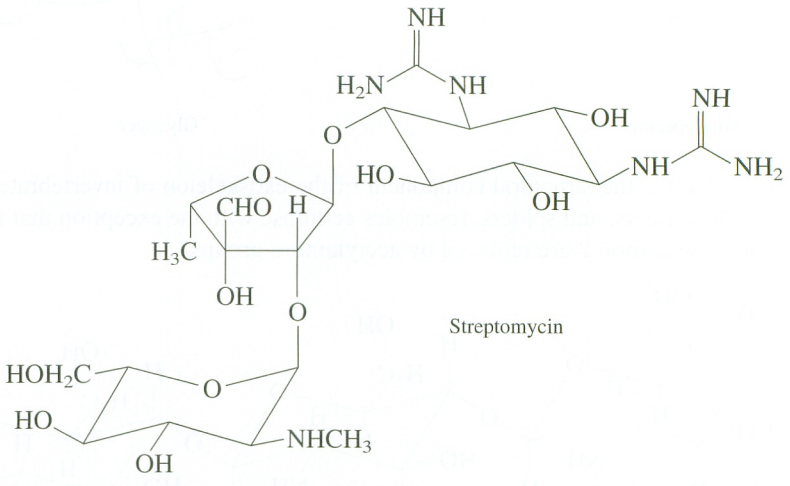
25.8 Other Carbohydrate-Containing Compounds

In addition to the sugars already described, many other naturally occurring compounds have related structures or have carbohydrate groups as part of a larger structure. There are too many of these to list completely, so only a few examples are provided here.

Sugars that have an amino group in place of a hydroxy group are widely distributed. For example, the aminosugars D-glucosamine and D-galactosamine are components of chitin and numerous other biologically important polysaccharides. Sugars that have a hydroxy group replaced with a hydrogen, called deoxy sugars, are important also. The monosaccharide D-2-deoxyribose is part of the polymer that stores genetic information, deoxyribose nucleic acid (DNA). And many antibiotics are derived from carbohydrates. Streptomycin is one example.

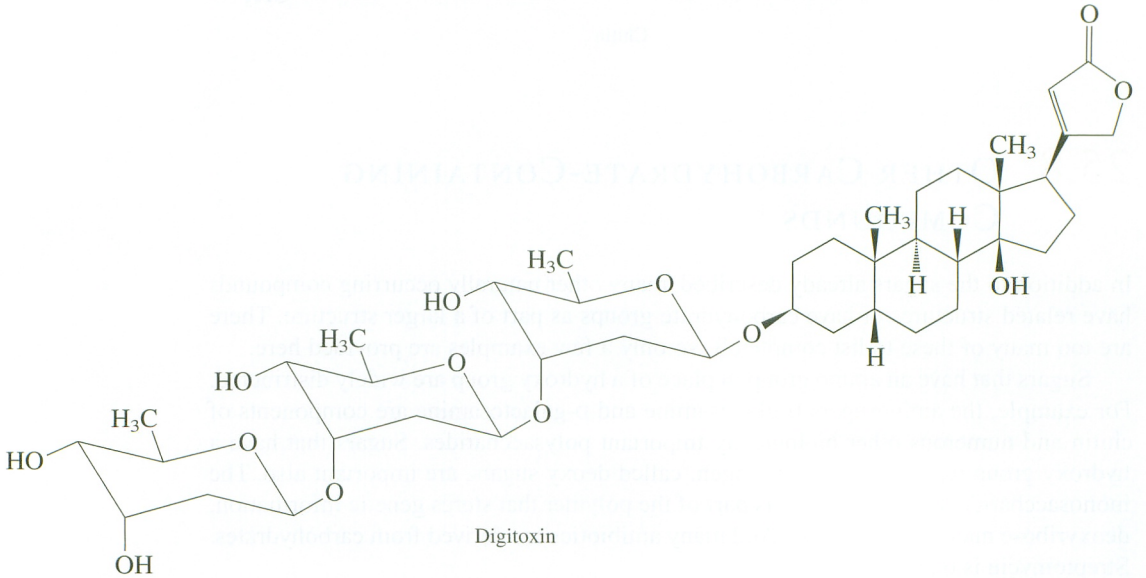


D-Glucosamine D-Galactosamine D-2-Deoxyribose



Streptomycin

Digitoxin, a cardiac glycoside that affects the action of the heart, is a complex glycoside formed from three units of the monosaccharide D-digitoxose and the steroidal (see Chapter 28) aglycone digitoxigenin. Small doses of digitoxin reduce the pulse rate, regularize the rhythm of the heart, and strengthen the heartbeat. In larger doses it is a powerful heart poison.

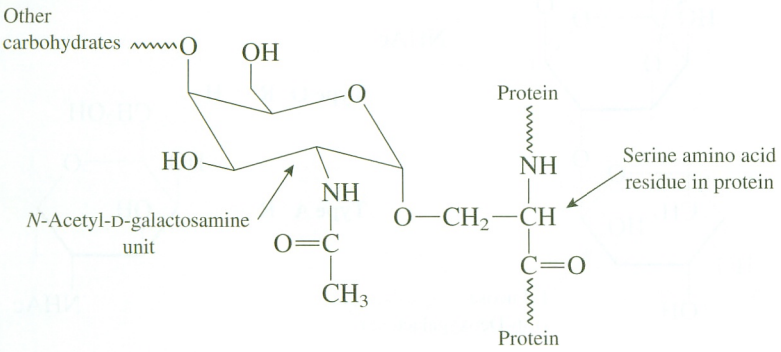


Digitoxin

PROBLEM 25.25

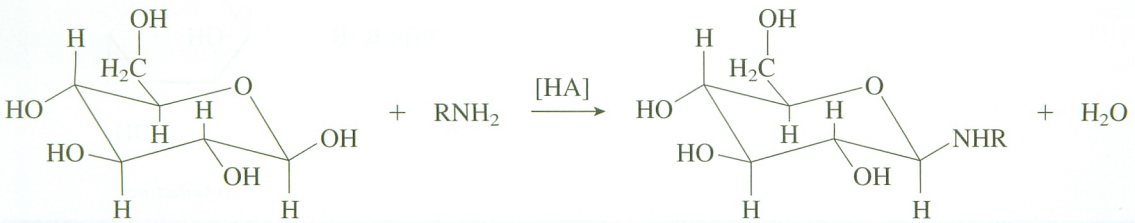
Show the structure of D-digitoxose. What unusual features are present in this monosaccharide?

Many proteins have short carbohydrate chains bonded to them. These **glycoproteins** have their carbohydrate groups linked to the protein chain by a glycosidic bond involving the nitrogen of the amide group of an asparagine amino acid residue or the oxygen of the hydroxy group of a serine or a threonine amino acid residue. The sugar chains are usually branched, so a wide variety of carbohydrate groups are possible. In most cases the sugar groups do not seem to have much effect on the biochemical properties of the protein. Instead, they seem to act as markers so that the proteins can be recognized for a variety of biological processes. An example of an *N*-acetyl-D-galactosamine attached to a protein through the hydroxy group of a serine amino acid residue is shown in the following structure:



PROBLEM 25.26

Carbohydrates can also attach to proteins through an amino group. A general example is shown in the following equation. Show the steps in the mechanism for this reaction.



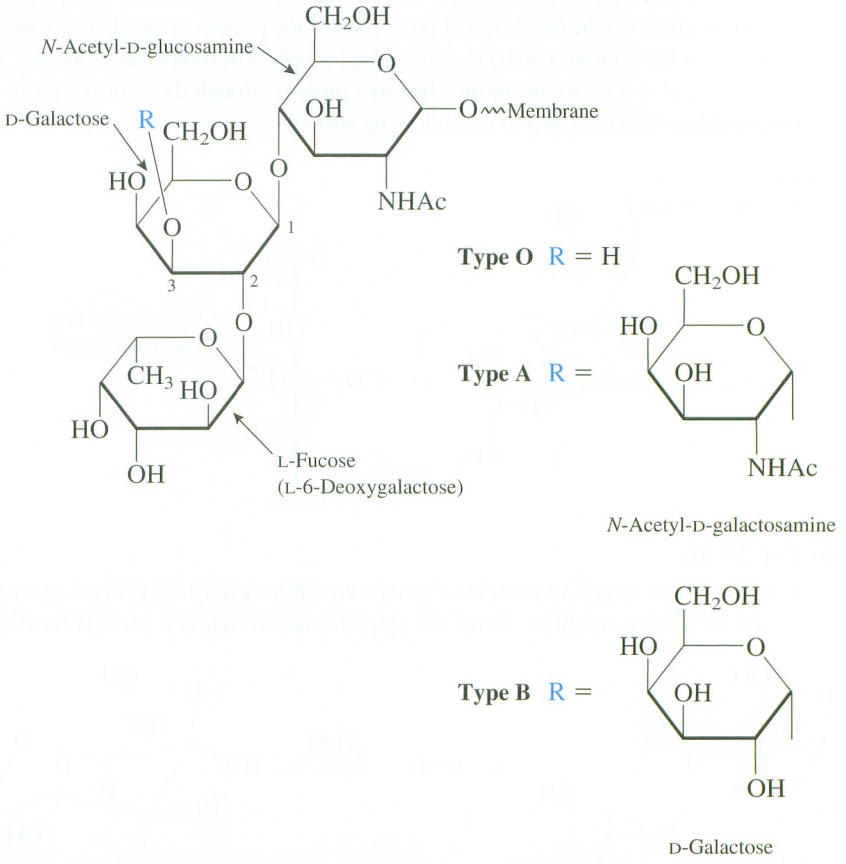
Focus On Biological Chemistry

Blood Groups

Lipids and proteins that are part of cell membranes often are bonded to small polysaccharide groups that project from the surface of the cell. Slight differences in the structures of polysaccharides that are bonded to lipids in red blood cell membranes of humans are responsible for the A, B, and O blood types. Antibodies recognize these groups and cause cells to clump when their surface groups are not the same as those on the cells of the original individual.

Continued

The structures of the ends of the polysaccharide chains of the blood group determinants are shown in the following diagram. For all of the blood types, the end of the polysaccharide chain has the hydroxy group on carbon 4 of an *N*-acetyl-D-glucosamine connected via a glycosidic bond to a D-galactose. The hydroxy group on carbon 2 of the D-galactose is connected to an unusual sugar, L-fucose (L-6-deoxygalactose), by a glycosidic bond. The only difference in the blood groups is the nature of the group, shown as R in the diagram, that is attached to the oxygen on carbon 3 of the D-galactose ring. For Type O, R is a hydrogen; for Type A, R is an *N*-acetyl-D-galactosamine; and for Type B, R is a D-galactose.



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Review of Mastery Goals

After completing this chapter, you should be able to:

- Show the general structures for carbohydrates including the variations that occur.
- Discuss the stereochemistry of carbohydrates, including the use of D or L to designate absolute stereochemistry. (Problem 25.33)
- Understand the cyclization of monosaccharides to form pyranose and furanose rings. (Problems 25.29, 25.30, 25.31, 25.36, and 25.44)
- Show the products of the common reactions of monosaccharides that were presented in this chapter: oxidation with nitric acid, oxidation with bromine, reduction with

sodium borohydride, esterification, glycoside formation, and the Kiliani-Fischer synthesis. (Problems 25.27 and 25.34)

- Understand Fischer's structure proof for glucose and apply this type of reasoning to other stereochemical problems. (Problems 25.35, 25.40, 25.42, 25.43, and 25.50)
- Understand the general structural features of disaccharides and polysaccharides. (Problem 25.47)

Additional Problems

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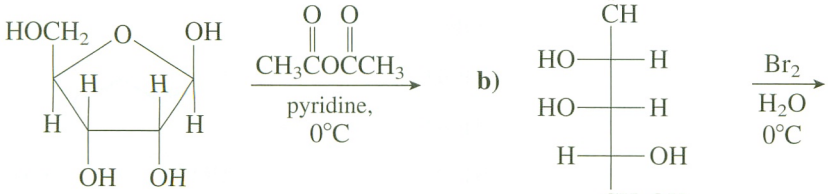
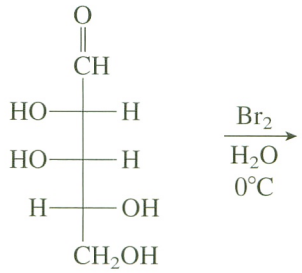
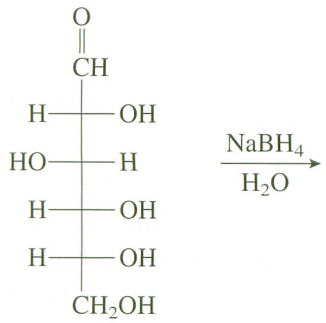
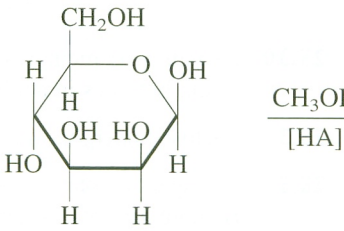
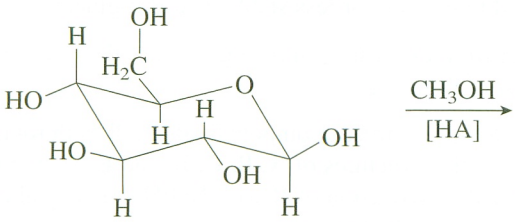
25.27 Show the products of these reactions:

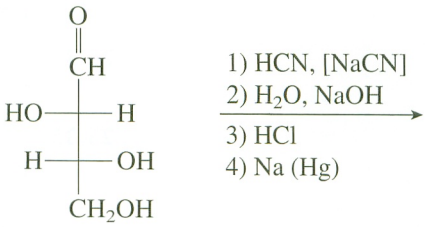
a) 

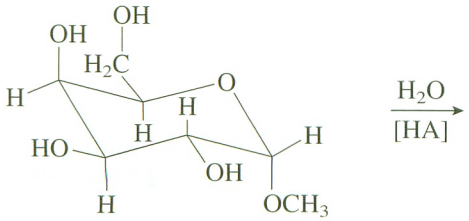
b) 

c) 

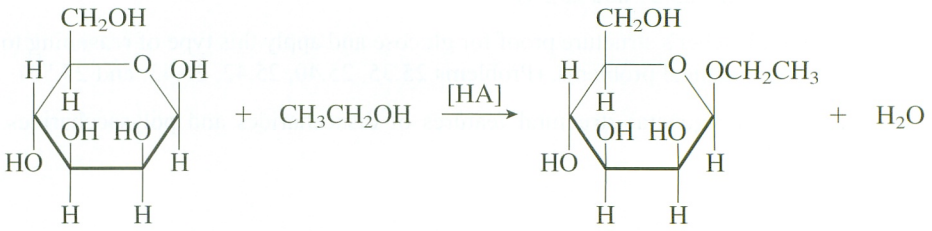
d) 

e) 

f) 

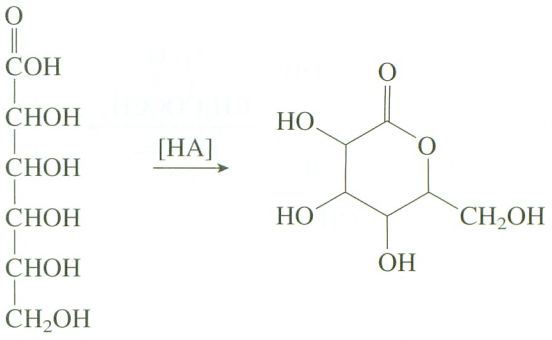
g) 

25.28 Show a mechanism for this reaction:



β-Mannose

25.29 Show a mechanism for this reaction:



25.30 Explain why methyl-α-D-glucoside does not exhibit mutarotation in basic solution but does in acidic solution.

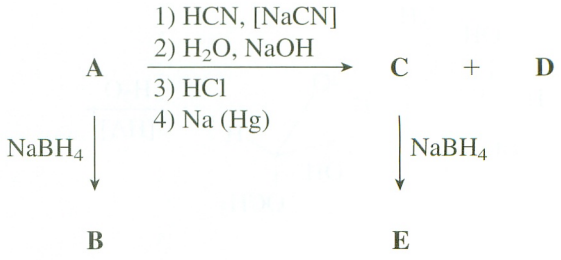
25.31 Lactose undergoes mutarotation in basic solution but sucrose does not. Explain.

25.32 The specific rotation of α-D-galactopyranose is +150.7, and that of the β-anomer is +52.8. The rotation of an equilibrium mixture of these two anomers is +80.2. Calculate the percentage of each in the equilibrium mixture.

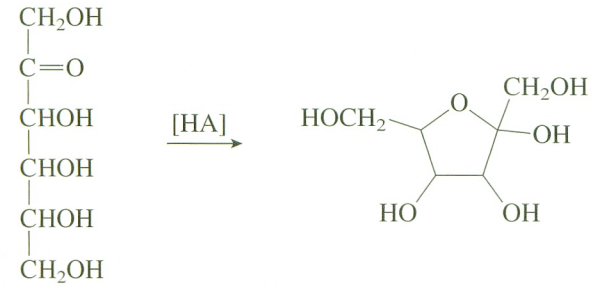
25.33 Draw the chair conformation of β-D-allopyranose. Explain whether you expect this compound to be more or less stable than β-D-glucopyranose.

25.34 How is the product from the reduction of D-glucose with $NaBH_4$ related to that from reduction of D-gulose?

25.35 Carbohydrate **A** is a D-aldotetrose. Compounds **B** and **E** both rotate plane-polarized light. Show the structures of **A, B, C, D,** and **E**. Show the structure of the product formed on reduction of **D** with $NaBH_4$ and explain whether or not it rotates plane-polarized light.



25.36 Show a mechanism for the conversion of D-fructose to a furanose. Do not worry about the stereochemistry of the reaction.



25.37 The interconversion of α-D-glucopyranose and β-D-glucopyranose can occur in aqueous solution without passing through the open aldehyde form. Show a mechanism for this process. (Use acid catalysis.)

25.38 Assign the configuration of each of the stereocenters of these compounds as *R* or *S*.

a) D-Galactose **b)** D-Ribose **c)** L-Xylose

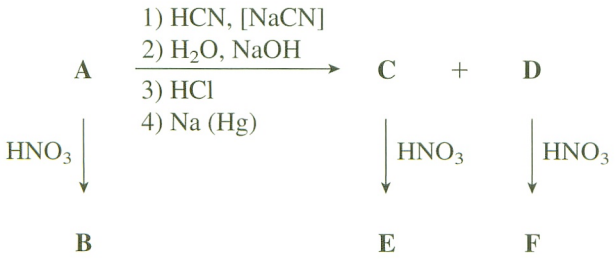
25.39 Show a mechanism for the interconversion of D-allose and D-altrose in aqueous base.

25.40 Explain how the Kiliani-Fischer synthesis could be used to demonstrate that naturally occurring glucose has the D-configuration, that is, that it has the same relative configuration at C-5 as does D-glyceraldehyde at C-2.

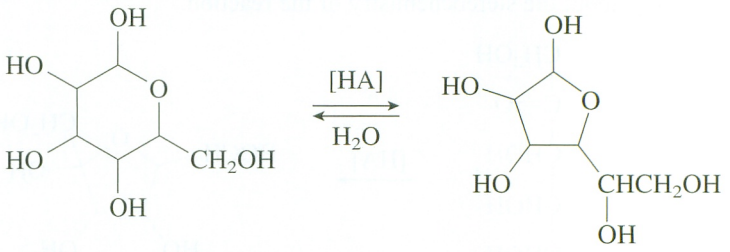
25.41 What aldohexose could be formed from D-galactose on treatment with base? Show a mechanism for the formation of this aldohexose.

25.42 A D-aldopentose, **X,** gives a product that rotates plane-polarized light on reaction with HNO_3. Compound **X** can be prepared from aldotetrose **Y** by Kiliani-Fischer synthesis. Reaction of **Y** with HNO_3 gives a product that rotates plane-polarized light. Show the structures of **X** and **Y.**

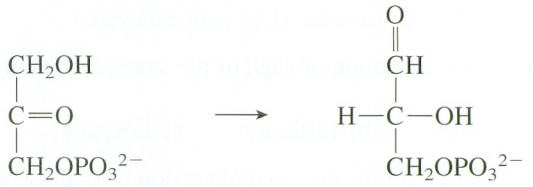
25.43 Compound **A** is a D-aldopentose. Compound **E** rotates plane-polarized light, whereas compounds **B** and **F** do not. Show the structures of **A, B, C, D, E,** and **F.**



25.44 Show a mechanism for this reaction:



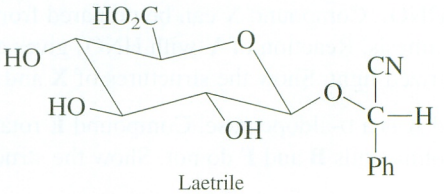
25.45 Dihydroxyacetone phosphate is converted to D-glyceraldehyde 3-phosphate by the enzyme triosephosphate isomerase as part of the glycolytic pathway of metabolism. Show how this interconversion could occur by a base-catalyzed mechanism:



Dihydroxyacetone phosphate

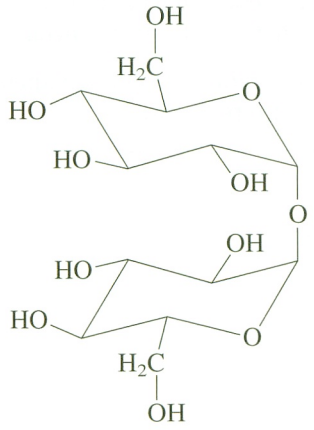
D-Glyceraldehyde 3-phosphate

25.46 Laetrile, found in the seeds of apricots and bitter almonds, has considerable toxicity because it releases hydrogen cyanide on hydrolysis. It has been purported to be useful in the treatment of cancer, but controlled studies have shown no evidence of effectiveness. Show how hydrogen cyanide is produced on hydrolysis of laetrile.



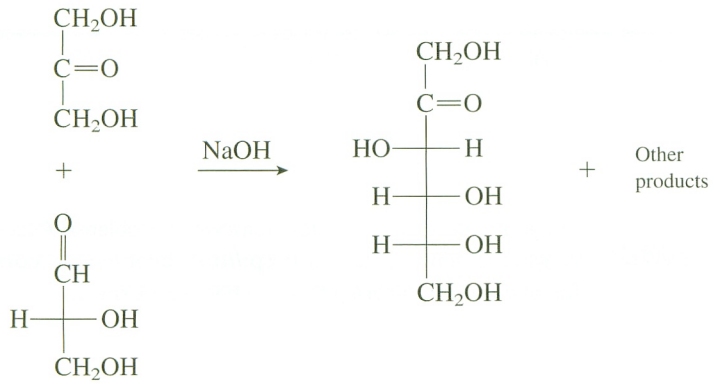
Laetrile

25.47 Trehalose is a disaccharide that is used by insects and some fungi to store energy. What monosaccharides are used to form trehalose? How are these monosaccharides connected? Is trehalose a reducing sugar?

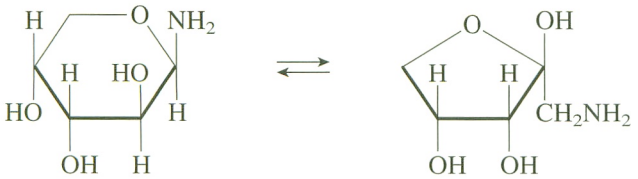


Trehalose

25.48 D-Glyceraldehyde, dihydroxyacetone, or a mixture of these two isomers reacts in the presence of sodium hydroxide to form fructose, along with other products. Show a mechanism for this reaction.



25.49 An example of the Amadori rearrangement is shown in the following equation. Suggest a mechanism for this reaction.

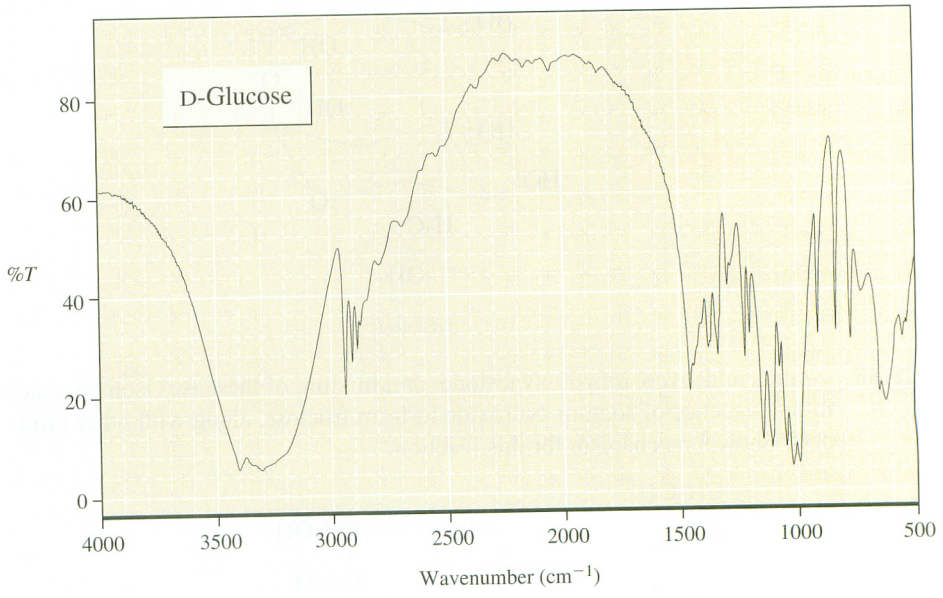


25.50 Two of the D-aldohexoses give the same product upon reduction with $NaBH_4$. Show the structures of these aldohexoses and the reduced product formed from them.

Problems Involving Spectroscopy

25.51 Explain why the NMR method described in the Focus On box "Determination of Anomer Configuration" on page 1095 cannot be used to determine the configurations of the anomers of D-mannopyranose.

25.52 The IR spectrum of D-glucose follows. Explain how this spectrum supports the cyclic structure for D-glucose.



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